

# Phytochemicals and Cancer Chemoprevention: Epigenetic Friends or Foe?

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## 1. Introduction

Cancer remains a major health problem and is responsible for one in eight deaths worldwide. 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. Despite the success of genome-wide association studies in identifying loci associated with cancer, a substantial proportion of the causality remains unexplained, leaving many questions how the remaining 'missing' heritability can be explained, although polygenic disease traits may account for some of these limitations (Maher, 2008; Manolio et al., 2009; Rakyan et al., 2011). Only a minority of cancers are caused by germline mutations, whereas the vast majority (90%) are linked to somatic mutations and environmental factors (Anand et al., 2008). Also, an estimated 55% increase in cancer incidence is expected by the year 2020 (Chaturvedi et al., 2011). 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. Observational studies have suggested that lifestyle risk factors such as tobacco, obesity, alcohol, sedentary lifestyle, high-fat diet, radiation, and infections are major contributors in cancer causes, which is further emphasized by the increase in cancer cases among immigrants from Asian to Western countries (Anand et al., 2008; Messina & Hilakivi-Clarke, 2009; Shu et al., 2009)). Reciprocally, a reasonable good fraction of cancer deaths may be prevented by modifying the diet composition (i.e. content of fiber, fruit, vegetable, fat/oil, protein, spices, cereals, etc.) and regular physical exercise (Anand et al., 2008; Bingham & Riboli, 2004; Boffetta et al., 2010; Tennant et al., 2010). 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 adaptative responses, metabolism, immune homeostasis and the physiology of the body.

The contribution of epigenetic changes (epimutations) in cancer 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 (Chi et al., 2010; Davalos & Esteller, 2010; Guil & Esteller, 2009; B. M. Lee & Mahadevan, 2009; Vanden Berghe et al., 2006b). Furthermore, many activities controlling chromatin dynamics require metabolites that shuttle between different cellular functions and pathways. One critical facet of histone and DNA modifying enzymes is that their activity also depends on intracellular levels of essential metabolites (acetyl-coA, Fe, ketoglutarate, NAD<sup>+</sup>, S-adenosylmethionine, see Figure 1) of which the concentrations are tightly linked to global cellular metabolism and energy levels (Bellet & Sassone-Corsi, 2010; Chang et al., 2010; Ladurner, 2009; Luo & Kuo, 2009; Wallace, 2010a; 2010b). Gene regulation is thus linked to the metabolic status of cells. To maintain uncontrolled cell proliferation of cancer cells, energy metabolism needs to be adjusted in order to fuel cell growth and invasion. In contrast to "healthy" cells which mainly generate energy from oxidative breakdown of pyruvate, cancer cell reprogram their glucose metabolism, limiting their energy metabolism largely to glycolysis. The fundamental difference in ratio of glycolysis to mitochondrial respiration between normal and cancerous cells is also known as the Warburg effect. As such, dynamic changes in energy levels and metabolite concentrations in the inflammatory tumor microenvironment can have significant epigenetic changes through variable activity of cofactor enzymes (Bonuccelli et al., 2010; Figueroa et al., 2010; Martinez-Outschoorn et al., 2011; Rathmell & Newgard, 2009; Teperino et al., 2010; Wellen et al., 2009).

The combinatorial nature of DNA methylation and histone modifications significantly extends the information potential of the genetic cancer code (Brower, 2011)(Figure 2). The most studied epigenetic lesion, which is DNA hypermethylation at the promoter region of many genes (Esteller, 2007; Mulero-Navarro & Esteller, 2008), is proved to be responsible for silencing of more than 600 cancer-related genes and this number is still rising. Besides effects on tumour suppressor genes, DNA methylation changes have also been detected in oncogenes as well as genes involved in the cell-cycle regulation, DNA repair, angiogenesis, metastasis and apoptosis (Herceg, 2007). Also oxidative stress (ROS, RNS) 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 (B. B. Aggarwal, 2009; B. B. Aggarwal & Gehlot, 2009; S. I. Grivennikov & Karin, 2010). 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 (Esteller, 2008). Epigenetic defects in DNA methylation patterns at CpG sites (epimutations), abnormalities in histone modifications, chromatin remodelling and noncoding RNAs (microRNA, long noncoding RNA) or corrupt chromatin states of tumor suppressor genes or oncogenes recently emerged as major governing factors in tumor progression and cancer drug sensitivity (Backdahl et al., 2009; Davalos & Esteller, 2010; Esteller, 2007; 2008; Guil & Esteller, 2009; Hesson et al., 2010; Lai & Wade, 2011; Lujambio et al., 2008; Lujambio & Esteller, 2007; Vanden Berghe et al., 2006b). In addition, genetic mutations of epigenetic modifying ("writer") enzymes add another level of regulatory complexity (Chi et al., 2010; Dalglish et al., 2010; Delhommeau et al., 2009; Elsasser et al., 2011; Ko et al., 2010; Varela et al., 2011). Recent advances in genomic technologies have initiated large-scale studies to map cancer-associated epigenetic variation, specifically variation in DNA methylation and

chromatin states (Berdasco & Esteller, 2010; Birney et al., 2007; Brower, 2011; Ernst & Kellis, 2010; Ernst et al., 2011; Myers et al., 2011; Rakyan et al., 2011; Raney et al., 2011). Given the prevalence of reversible epigenetic abnormalities in different cancers, epigenetic therapy holds great promise for treatment. The future of specific and effective epigenetic drug design will rely on our ability in understanding epigenomic landscapes in normal and cancerous disease states (Hakim et al., 2011; Christopher A. Hamm & Costa, 2011; Gioacchino Natoli, 2010; G. Natoli et al., 2011; Tolhuis et al., 2011; B. van Steensel, 2011).

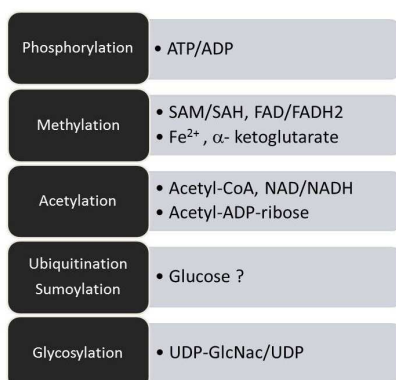


Fig. 1. Coupling of cancer metabolism, diet and epigenetics

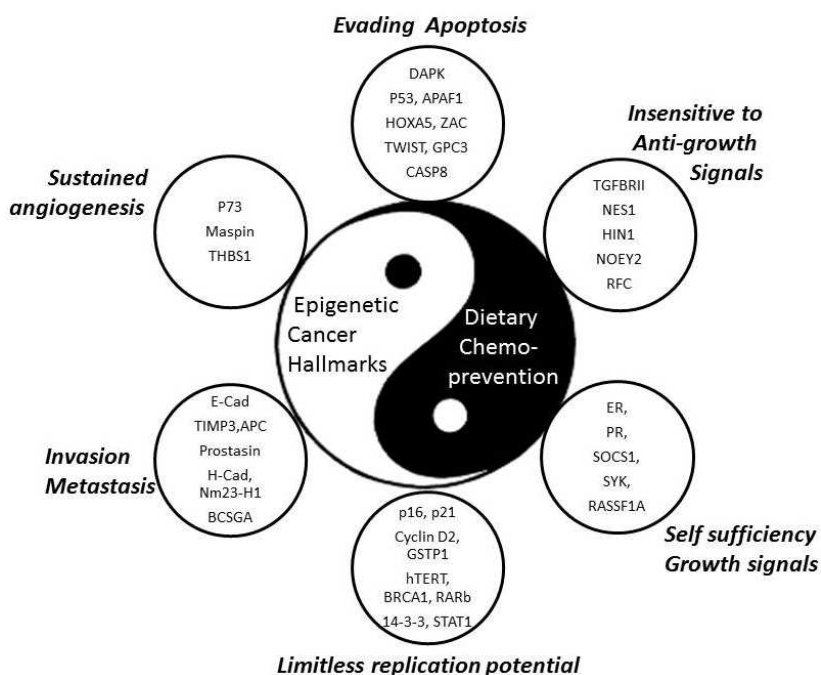


Fig. 2. Dietary reversal of epigenetic changes in cancer cells

Once critical facet of histone modifications is that they are elicited by specific enzymatic activities that depend on the intracellular levels of essential metabolites: these metabolites sense cellular metabolism, nutrients and energy levels in the cell.

Changes in DNA methylation have been recognized as one of the most common molecular alterations in human neoplasia and hypermethylation of gene-promoter regions is being revealed as one of the most frequent mechanisms of loss of gene function. This figure summarizes how changes in DNA-methylation (epimutations) contribute to the 6 hallmarks of a cancer cell i.e. limitless replicative potential, self-sufficiency in growth signals, insensitivity to growth-inhibitory signals, evasion of programmed cell death, sustained angiogenesis and tissue invasion and metastasis. Since epigenetic changes (epimutations) are more easily reversible (when compared with genetic mutations), this has inspired various research efforts aiming to identify dietary phytochemicals (nutri-epigenomics) which can reverse epimutations and/or prevent cancer progression.

## 2. Dietary chemoprevention of cancer-inflammation

Cancer cells are distinguished by several distinct characteristics, such as self-sufficiency in growth signal, resistance to growth inhibition, limitless replicative potential, evasion of apoptosis, sustained angiogenesis, and tissue invasion and metastasis (Hanahan & Weinberg, 2011) (Figure 2). Tumor cells acquire these properties due to the dysregulation of multiple genes and associated cell signaling pathways, most of which are linked to inflammation. Immune cells also infiltrate in tumors, engage in an extensive and dynamic crosstalk with cancer cells (B. B. Aggarwal, 2009; S. I. Grivennikov et al., 2010a; Mantovani et al., 2008). Inflammation also affects immune surveillance and responses to therapy (D. Iliopoulos et al., 2011; M. Liu et al., 2010a; Rajasekhar et al., 2011; S. V. Sharma et al., 2010).

For that reason, rationally designed drugs that target a single gene product are unlikely to be of use in preventing or treating cancer. Moreover, targeted drugs can cause serious and even life-threatening side effects or therapy resistance (Hanahan & Weinberg, 2011). When a complex system starts to dysfunction, it is generally best to fix it early. Often, cancers have a long latency period –often 20 years or more-. By the time they are clinically detectable, the system has degenerated into a disorganized, chaotic mess at which point it may be beyond repair (Sporn, 2011). Therefore, there is an urgent need for safe and effective chemopreventive multifunctional drugs that act at entire networks in the body, rather than single targets (Deocaris et al., 2008). The basic idea of cancer chemoprevention is to arrest or reverse the progression of premalignant cells towards full malignancy using physiological mechanisms that do not kill healthy cells, but attenuate cancer-inflammation (B. B. Aggarwal & Gehlot, 2009; Anand et al., 2008; Jirtle & Skinner, 2007; Surh, 2003)(Figure 3).

The global demand for more affordable therapeutics and concerns about side effects of commonly used drugs has renewed interest in phytochemicals and traditional medicines which allow chronic use (Harvey, 2008; J. W. H. Li & Vederas, 2009; Singh, 2007). Studies on a wide spectrum of plant secondary metabolites extractable as natural products from fruits, vegetables, teas, spices, and traditional medicinal herbs have identified various bioactive plant phytochemicals that regulate multiple cancer-inflammation pathways and epigenetic cofactors, are cost effective, exhibit low toxicity, and are readily available (B. B. Aggarwal et al., 2011; Deorukhkar et al., 2007; Ki Won Lee et al., 2011; Yang & Dou, 2010). The recent

advances in genomics and metabolomics have enabled biologists to better investigate the potential use of immunomodulatory natural products for treatment or control of cancerous diseases. More recently, evidence is emerging that specific combinations of phytochemicals maybe far more effective in protecting against cancer than isolated compounds (Harvey, 2008; Kok et al., 2008). The cancer preventive or protective activities of the various immunomodulatory natural products lie in their effects on cellular defenses including detoxifying and antioxidant enzyme systems, and the induction of anti-inflammatory and antitumor or antimetastasis responses, often by targeting specific key transcription factors (i.e. like nuclear factor kappa B (NFκB), activator protein (AP-1), signal transducers and activators of transcription (STAT3), nuclear factor erythroid 2-related factor (NRF2), peroxisome proliferator-activated receptor-  $\gamma$  (PPAR  $\gamma$ ), estrogen receptor, liver X receptor (LXR), hypoxia inducible factor-1 (HIF-1)), epigenetic cofactors and microRNAs which are involved in tumor progression (Figure 4) (Meeran et al., 2010; Parasramka et al., 2011; Szarc vel Szcic et al., 2010). Typically, dysregulation of transcription factor activity is the result of numerous mechanisms, such as changes in gene expression, protein - protein interactions and post-translational modifications, leading to deregulation of gene products that are involved in both inflammation and carcinogenesis. Remarkably, "transient" inflammatory pathways can also trigger mitotic stable epigenetic switches from nontransformed to metastatic cancer cells via feedback signaling involving NFκB and Stat3 transcription factors, Lin28 and let-7 microRNAs and the cytokine IL6 in the tumor microenvironment (D. Iliopoulos et al., 2009; D. Iliopoulos et al., 2010). Furthermore, emerging data demonstrate the direct influence of certain anti-inflammatory dietary factors (for example polyphenols,

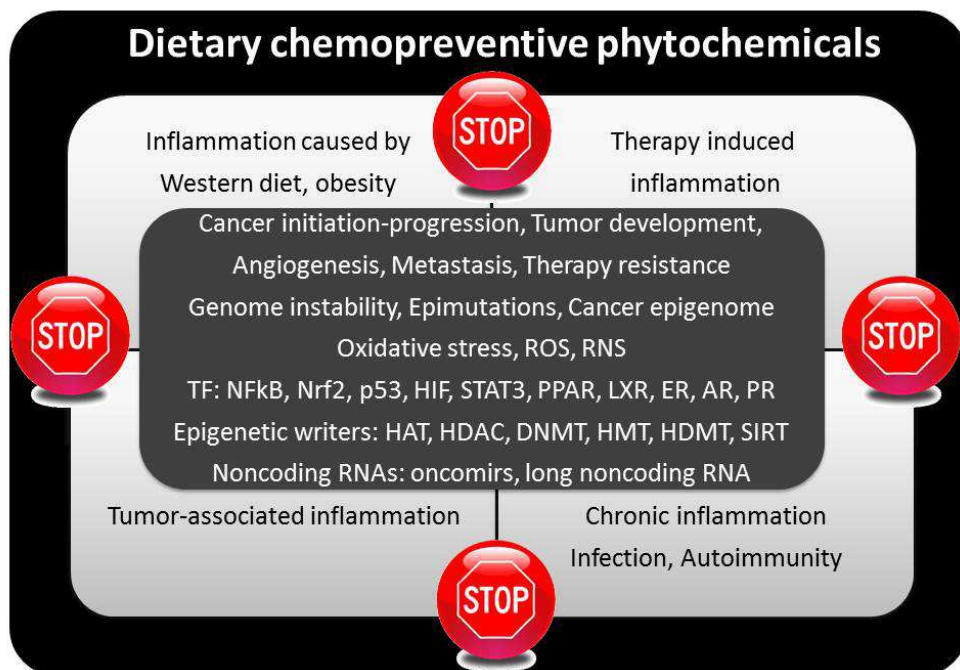


Fig. 3. Dietary chemoprevention of cancer-inflammation

isothiocyanates, epicatechins) and micronutrients (for example folic acid, selenium) on heritable gene expression, activity of the epigenetic machinery, DNA methylation or chromatin remodelling (Burdge & Lillycrop, 2010; Delage & Dashwood, 2008; Fang et al., 2007; Folmer et al., 2010; Hauser & Jung, 2008; Kirk et al., 2008; Kontogiorgis et al., 2010; Link et al., 2010; Suzuki & Miyata, 2006, Szarc vel Szic et al., 2010). Because epigenetic changes are reversible, developing drugs that control epigenetic regulation now attracts substantial research investment, including the development of functional foods or supplements as nutrition based epigenetic modulators for cancer chemoprevention (2008; Arasaradnam et al., 2008; Bingham & Riboli, 2004; Dashwood & Ho, 2007; Dashwood et al., 2006; Hurt & Farrar, 2008; Kawasaki et al., 2008; b; Parasramka et al., 2011; Szarc vel Szic et al., 2010)

The basic idea of cancer chemoprevention by dietary phytochemicals is to arrest or reverse the progression of premalignant cells towards full malignancy using physiological mechanisms by attenuating cancer-inflammation pathways. Chronic inflammation associated with infections or autoimmune disease precedes tumor development and can contribute to it through induction of oncogenic mutations, genomic instability, epimutations, changed expression of epigenetic "writer-reader-eraser" enzymes, oncomirs and long noncoding RNAs affecting early tumor promotion, and enhanced angiogenesis. Prolonged exposure to environmental irritants, Western diet or obesity can also result in low-grade chronic inflammation that precedes tumor development and contributes to it through the mechanisms mentioned above. Tumor-associated inflammation goes hand in hand with tumor development. This inflammatory response can enhance neoangiogenesis, promote tumor progression and metastatic spread, cause local immunosuppression, and further augment genomic instability. Cancer therapy can also trigger an inflammatory response by causing trauma, necrosis, and tissue injury that stimulate tumor re-emergence and resistance to therapy. However, in some cases, therapy-induced inflammation can enhance antigen presentation, leading to immune-mediated tumor eradication.

### 3. Chromatin states and methylomes in the epigenomic landscape

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. 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 (Chi et al., 2010). This structural restriction of silenced chromatin on gene expression can be overcome by chromatin cofactor complexes, which remodel nucleosomes along the DNA or reversibly modify (acetylation, phosphorylation, ubiquitylation, glycosylation, sumoylation) histones on lysine, arginine, serine or threonine residues of amino-terminal histone tails. Since the discovery of histone-modifying enzymes, N-terminal histone tails protruding from nucleosomes were found to be 'velcro patches' for polycomb proteins, (de)acetylases (HDAC/HAT), (de)methylases (HMT/HDMT), ubiquitin

ligases, small ubiquitin-related modifier (SUMO) ligases, kinases, phosphatases, ribosylases, which together establish specific chromatin states involved in transcription (Chi et al., 2010; Ernst & Kellis, 2010; Ernst et al., 2011). 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" (Chi et al., 2010). Based on coexisting histone marks and genomewide ChIP-seq data available within the ENCODE consortium, principal component analysis allowed to reduce the complexity of the histone code into 9 different chromatin states with different functional regulatory features (Ernst & Kellis, 2010; Ernst et al., 2011).

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 (Brenner et al., 2005; Gupta et al., 2010; Hervouet et al., 2009; Perissi et al., 2010; Vire et al., 2006). 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 expression and other chromatin functions (Fischle, 2008; Schreiber & Bernstein, 2002; Seet et al., 2006). The dynamic time-dependent combinations of histone modifications or threedimensional locus configuration further increase the complexity of information contained in chromatin (Bickmore et al., 2011; Chi et al., 2010; Fischle, 2008; G. Natoli, 2010; G. Natoli et al., 2011; Schreiber & Bernstein, 2002; B. van Steensel, 2011).

DNA methylation is the best known epigenetic mark (Bird, 2002; Esteller, 2007). It is catalyzed by two types of DNMTs: DNMT1 is a maintenance methyltransferase, whereas both DNMT3A and DNMT3B are *de novo* methyltransferases (P. A. Jones & Liang, 2009; Law & Jacobsen, 2010). 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 (Lees-Murdock & Walsh, 2008), X-chromosome inactivation (K. D. Robertson, 2005) and silencing of repetitive sequences (Miranda & Jones, 2007). 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 functional maintenance methylation pathways, or actively, by removing methylated cytosines. In plants active demethylation is achieved 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 may be 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 (Law & Jacobsen, 2010). Of particular interest, ROS and oxidative stress may affect DNA demethylation by DNA oxidation or TET-mediated DNA hydroxymethylation (Perillo et al., 2008; Luan Wang et al., 2011).

Although DNA methylation is the best-known epigenetic mark (P. A. Jones & Liang, 2009; Lande-Diner & Cedar, 2005; Scarano et al., 2005), DNA methylation does not act alone. It occurs in the context of nucleosome positioning, DNA sequence composition and histone modifications (Chodavarapu et al., 2010; B. M. Lee & Mahadevan, 2009; Vaissiere et al., 2008). 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 (Chodavarapu et al., 2010). 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 combinatorial histone code is a matter of debate (Chi et al., 2010; Cosgrove & Wolberger, 2005; Fischle, 2008; Guil & Esteller, 2009; Jenuwein & Allis, 2001; B. M. Lee & Mahadevan, 2009; Margueron et al., 2005), 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 (R. S. Jones, 2007; A. G. Robertson et al., 2008). 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 (Perissi et al., 2010; Perissi & Rosenfeld, 2005). Altogether, "histone code" may only become biologically meaningful at the level of domains 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 (Chi et al., 2010; Fujioka et al., 2009; Nolis et al., 2009; Nunez et al., 2009; B. van Steensel, 2011). 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) (Lieberman-Aiden et al., 2009; Metivier et al., 2006; G. Natoli, 2010; G. Natoli et al., 2011; Nolis et al., 2009; Nunez et al., 2009; Bas van Steensel, 2011).

There is good evidence that also noncoding RNAs regulate chromatin architecture (Guil & Esteller, 2009; Gupta et al., 2010; Mattick et al., 2009a; Mattick et al., 2009b; Taft et al., 2009a; Taft et al., 2009b; Tsai et al., 2010). 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 (Gupta et al., 2010; Mattick et al., 2009b; Taft et al., 2009a; Taft et al., 2009b). 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 (De Santa et al., 2010). RNA regulatory networks may determine most of our complex characteristics and play a significant role in disease (De Santa et al., 2010). 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 (Denis et al., 2011; Guil & Esteller, 2009; Lujambio et al., 2008; Lujambio & Esteller, 2007; 2009; 'M.N. Ndlovu et al., 2011; Parasramka et al., 2011). Alternatively, long ncRNAs and tiRNAs can regulate gene expression and/or DNA methylation by promoter association (De Santa et al., 2010; Gupta et al., 2010; Taft et al., 2009a; Taft et al., 2009b; Tsai et al., 2010). DNA-methylation can thus also be RNA-directed (Denis et al., 2011; Guil & Esteller, 2009; Mahfouz; 'M.N. Ndlovu et al., 2011).

#### **4. Immunity, cancer-inflammation and the epigenomic landscape**

Pathologists have long recognized that some tumors are densely infiltrated by cell of both the innate and adaptive arms of the immune system and thereby mirror inflammatory conditions arising in non-neoplastic tissues (Hanahan & Weinberg, 2011). Originally, these immune responses were believed to eradicate tumors, which to some extent is true, although this pressure on the tumor triggers some escape programs to evade immune destruction. As such, solid tumors that do appear have somehow managed to avoid detection by the various arms of the immune system or have been able to limit the extent of immunological killing, thereby evading eradication. For example, cancer cells may paralyze infiltrating CTLs and NK cells, by secreting TGF $\beta$  or other immunosuppressive factors. As such, immunoevasion can be considered as an emerging hallmark of carcinogenesis.

Furthermore, since 2000, various clues were reported that the tumor-associated inflammatory response had the unanticipated, paradoxical effect of enhancing tumorigenesis and progression (B. B. Aggarwal, 2009; B. B. Aggarwal & Gehlot, 2009; S.I. Grivennikov & Karin, 2010a& c; Ning Li et al., 2011; Naugler & Karin, 2008). Inflammation contributes to cancer progression by supplying bioactive molecules to its microenvironment, including growth factors that sustain proliferative signaling, survival factors that limit cell death, proangiogenic factors, extracellular matrix-modifying enzymes that facilitate angiogenesis, invasion and metastasis, and signals that trigger activation of endothelial mesenchymal transition (S.I. Grivennikov et al., 2010b). The complexity of the inflammatory response requires that its many functional programs are controlled coordinately in some situations but independently in others (Medzhitov & Hornig, 2009; Pasparakis, 2009). 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.

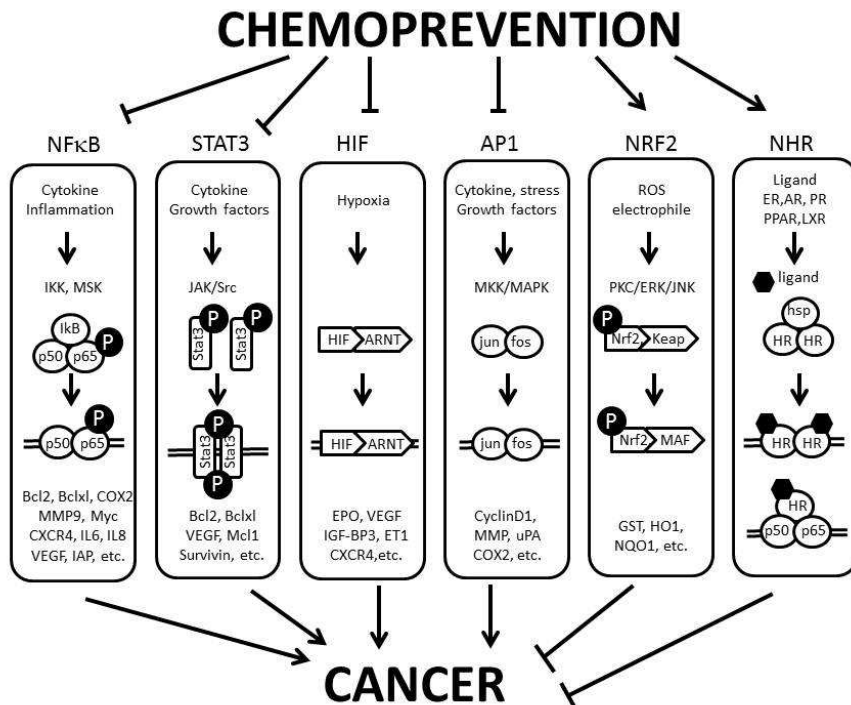
#### **4.1 Cell specific mechanisms in the tumor microenvironment**

Today, tumors are increasingly recognized as organs which can only be understood by studying the individual specialized cell types within it as well as the tumor microenvironment. Besides cancer cells, the parenchyma and stroma of tumors contain cancer stem cells, immune cells, endothelial cells, invasive cancer cells, cancer-associated fibroblasts that collectively enable tumor growth and progression. Cell-specific mechanisms operate at the level of different cell types, and include regulation of their recruitment and activation. The most frequently found immune cells within the tumor microenvironment are tumor-associated macrophages (TAMs) and T cells and are an important source of cytokines (Balkwill et al., 2005; Balkwill & Mantovani, 2010; Mantovani et al., 2008). TAMs mostly promote tumor growth and may be obligatory for angiogenesis, invasion, and metastasis and high TAM content generally correlates with poor prognosis (B. B. Aggarwal & Gehlot, 2009; Balkwill et al., 2005; Balkwill & Mantovani, 2010; S. I. Grivennikov & Karin, 2010b). Moreover, most cancers contain an inflammatory infiltrate that is hijacked by tumor cells to promote angiogenesis, tissue invasion and cell proliferation. Also, overnutrition and obesity activate the immune system which at long-term switches to chronic inflammatory condition which is a fertile soil for cancer development (Bharat B. Aggarwal, 2010; Anand et al., 2008; Hotamisligil, 2010; Mandl et al., 2009; Olefsky, 2009; E. J. Park et al., 2010; Solinas & Karin, 2010; Zhang et al., 2008).

#### **4.2 Regulation of transcription factors in cancer-related inflammation**

Production of tumor-promoting cytokines by immune/inflammatory cells that activate transcription factors in premalignant cells to induce genes that stimulate cell proliferation and survival, is a major tumor promoting mechanism. Among all the mediators and cellular effectors of inflammation, NF $\kappa$ B is perhaps the central transcription factor, which regulates expression of more than 400 genes (Chaturvedi et al., 2011; L. F. Chen & Greene, 2004; Ghosh & Hayden, 2008; Karin & Greten, 2005). NF $\kappa$ B family transcription factors 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. Furthermore, the NF $\kappa$ B pathway is regulated by many other pathways, i.e. EGFR/Her2-PI3K-Akt/IKK $\alpha$ , RSK2, MSK1, TP53 PTEN, Akt-mTOR, Ras, Raf, Wnt-catenin, hypoxia, oxidative stress (Chaturvedi et al., 2011). In nonstimulated cells, NF $\kappa$ B TFs are bound to inhibitory (I) $\kappa$ B proteins and are thereby sequestered in the cytoplasm. Activation leads to phosphorylation of I $\kappa$ B proteins and their subsequent recognition by ubiquitinating enzymes. The resulting proteasomal degradation of I $\kappa$ B proteins liberates NF $\kappa$ B transcription factors, which translocate to the nucleus to drive expression of target genes. Two protein kinases with a high degree of sequence similarity, I $\kappa$ B kinase (IKK) $\alpha$  and IKK $\beta$ ,

mediate phosphorylation of I $\kappa$ B proteins and represent a convergence point for most signal transduction pathways leading to NF $\kappa$ B activation. Most of the IKK $\alpha$  and IKK $\beta$  molecules in the cell are part of IKK complexes that also contain a regulatory subunit called IKK $\gamma$  or NF $\kappa$ B-essential modulator (NEMO). Alternative to IKK, various additional kinases have been identified which modulate transcriptional nuclear activity of NF $\kappa$ B, including mitogen- and stress-activated protein kinase (MSK), protein kinase (PK)Ac, phosphoinositide 3-kinases PI3K and AKT (L. F. Chen & Greene, 2004; Edmunds & Mahadevan, 2006; Vanden Berghe et al. 2011; Vermeulen et al., 2009; Vermeulen et al., 2003; Viatour et al., 2005). Members of the NF $\kappa$ B family of dimeric transcription factors regulate expression of a large number of genes involved in immune responses, inflammation, metabolic stress, cell survival, cell proliferation and cancer. 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 (S. I. Grivennikov & Karin, 2010b). Furthermore, constitutive activity of NF $\kappa$ B/IKK has been observed in many cancer cells, inflammatory disorders, obesity and insulin resistance (Arkan et al., 2005; Ghosh & Hayden, 2008; Hotamisligil, 2010; Karin, 2006; Karin & Greten, 2005; Mandl et al., 2009; Nakanishi & Toi, 2005; Olefsky, 2009; E. J. Park et al., 2010; Perkins, 2007). Besides constitutively activated NF $\kappa$ B found in several human cancer cell lines, including lymphomas and carcinomas of the breast, prostate, lung, colon, pancreas, head and neck and oesophagus, activated NF $\kappa$ B has also been noted in tissue samples from cancer patients (Baud & Karin, 2009; Chaturvedi et al., 2011; Dey et al., 2008). Studies of cancer-associated mutations have also reported that mutations in the upstream signal components of NF $\kappa$ B or p53 mutations could direct constitutive NF $\kappa$ B activation in cancer cell lines and patient samples (Dey et al., 2008; Dijsselbloem et al. 2007; Weisz et al., 2007). Therefore, inhibition of NF $\kappa$ B activity has been found to be a useful addition to chemotherapy regimens of a variety of cancers (Baud & Karin, 2009; Karin et al., 2004). Although quite a number of genes contain NF $\kappa$ B-responsive elements in their regulatory regions, their expression pattern can significantly vary from both a kinetic and quantitative point of view (Ghosh & Hayden, 2008; Hayden & Ghosh, 2008; Medzhitov & Horng, 2009; G. Natoli et al., 2005; O'Dea & Hoffmann, 2010; Perkins, 2007; Ramirez-Carrozzi et al., 2009; Vanden Berghe et al., 2006b; Werner et al., 2005). At the transcription level, selectivity is conferred by the expression or activation of specific NF $\kappa$ B subunits and their respective posttranslational modifications, and by combinatorial interactions between NF $\kappa$ B and other transcription factors, such as activator protein (AP-1), signal transducers and activators of transcription (STAT3), nuclear factor erythroid 2-related factor (NRF2), peroxisome proliferator-activated receptor- $\gamma$  (PPAR  $\gamma$ ), estrogen receptor (ER), liver X receptor (LXR), hypoxia inducible factor-1 (HIF-1), p53 which are involved in angiogenesis, chemoresistance, stem cell survival, cancer invasion and tumour progression (B. B. Aggarwal & Gehlot, 2009; Dey et al., 2008; Eferl & Wagner, 2003; Reuter et al., 2010; Rohwer et al., 2010; van Uden et al., 2011). Various naturally occurring phytochemicals such as withaferin, curcumin, resveratrol, mangiferin hold promise as anti-cancer drugs by interfering with NF $\kappa$ B, STAT3, AP1, HIF, PPAR, ER, LXR, p53 activities and gene expression programs (Dijsselbloem et al., 2007; Garcia-Rivera et al., 2011; Harvey, 2008; Kaileh et al. 2007; Kontogiorgis, C. et al. 2010; J. W. H. Li & Vederas, 2009; Surh, 2003; Vanden Berghe et al., 2006 & 2011; Suttana et al., 2010) (Figure 4)



Abbreviations used: ARE, antioxidant response element, ARNT, aryl hydrocarbon receptor nuclear translocator; NHR, nuclear hormone receptor; HRE, hypoxia responsive element; IKK, inhibitor of IκB kinase; Jak, Janus kinase, JNK; cjun N terminal kinase; MAPK, mitogen-activated protein kinase; STAT3, signal transducer and activator of transcription

Fig. 4. Modulation of tumor promoting transcription factor pathways by dietary phytochemicals (adapted from Sung et al. 2011).

### 4.3 Chromatin dynamics in cancer-inflammation

Since transcription factors bind very poorly or not at all to nucleosomal DNA, their activation is coordinated to recruitment of noncoding RNAs (Gupta et al., 2010; Tsai et al., 2010), DNMTs (Hervouet et al., 2009) and epigenetic writer, reader or eraser proteins (Chi et al., 2010), including 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 (Dong et al., 2008; Ghosh & Hayden, 2008; Perissi et al., 2010; Rosenfeld et al., 2006; Vanden Berghe et al., 2006b; Vermeulen et al., 2009). Parallel posttranslational modifications (phosphorylation, acetylation, methylation, ribosylation, sumoylation, ubiquitination) of histone and non-

histone transcription factor and cofactor complexes in response to signalling components allow displacement of polycomb complexes and formation of dynamic enhanceosome complexes which establish a distinct chromatin structure (Bracken & Helin, 2009; Dawson et al., 2009; Gehani et al., 2010; N. Ndlovu et al., 2009; Schreiber & Bernstein, 2002; Vanden Berghe et al., 1999a; Vermeulen et al., 2009; Vermeulen et al., 2003). These epigenetic settings are the ultimate integration sites of both environmental and differentiative inputs, determining proper expression of each target gene (Ford & Thanos, 2010; Ghosh & Hayden, 2008; Hayden & Ghosh, 2008; G. Natoli & De Santa, 2006; Vanden Berghe et al., 2006b). Investigation of epigenetic regulation of cancer-inflammation genes, revealed different subclasses according to chromatin activation mode and gene expression profile (Ramirez-Carrozzi et al., 2009; Ramirez-Carrozzi et al., 2006). 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, exhibit a strong bias toward activation of SWI/SNF-independent CpG-island genes. In contrast interferon (IFN) $\beta$  preferentially activates SWI/SNF-dependent non-CpG-island promoters. At the level of CpG methylation, changes in DNA methylation of IKK, I $\kappa$ B and RelB promoters (G. Maeda et al., 2007; O'Gorman et al., 2010; Puto & Reed, 2008) affect gene induction properties upon re-exposure to an inflammatory stimulus (Ashall et al., 2009; El-Osta et al., 2008; El Gazzar et al., 2009; El Gazzar et al., 2007; Puto & Reed, 2008). Furthermore, CpG-methylation of certain genes enables some cells to acquire new capabilities needed for tumorigenesis (Widschwendter & Jones, 2002)(Figure 2). Cells which accumulated DNA methylation at various loci as a function of time (age) and as a function of exposure to growth factors or chronic inflammation gain novel capabilities to promote carcinogenesis, i.e. limitless replicative potential, selfsufficiency in growth signals, insensitivity to growth-inhibitory signals, evasion of programmed cell death, sustained angiogenesis and tissue invasion and metastasis (Teschendorff et al., 2010; Widschwendter & Jones, 2002)(Figure 2).

## **5. Cancer-inflammation, cancer metabolism and epimutations: cause or consequence?**

Since inflammatory gene expression dynamics is highly dependent on epigenetic control mechanisms (De Santa et al., 2007; Medzhitov & Horng, 2009; MESSI et al., 2003; G. Natoli & De Santa, 2006; G. Natoli et al., 2005; Vanden Berghe et al., 2006b), we have previously characterized 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 (Gerlo et al., 2008; N. Ndlovu et al., 2009). Furthermore, recruitment of CBP/p300 acetylases and MSK kinase seems to prevent heterochromatinisation and recruitment of heterochromatin protein (HP)1 upon phosphoacetylation of transcription factor and histone components (Boeke et al., 2010; N. Ndlovu et al., 2009; Vanden Berghe et

al., 1999a; Vermeulen et al., 2009; Vermeulen et al., 2003). Along the same line, the kinase MSK kinase was found to displace polycomb repressor complexes during gene activation (Gehani et al., 2010). Interestingly, promoter-binding activity of Sp1 and AP1 Fra1 are responsible for priming IL6 promoter chromatin relaxation, which further promotes binding of NFκB transcription. 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 (Dijsselbloem et al., 2007; N. Ndlovu et al., 2009; Vanden Berghe et al., 2006a). Furthermore, 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 (Armenante et al., 1999; Dandrea et al., 2009). Similarly, various transcription factors (p53, cmyc, ER, GR, NFκB p65 and others) were found to recruit DNMTs and modulate promoter enhancer function in a time-dependent and signal specific fashion (Aaltonen et al., 2008; Brenner et al., 2005; Hervouet et al., 2009; Kangaspeska et al., 2008; Y. Liu et al., 2011; Metivier et al., 2008; Santourlidis et al., 2001; Wiench et al., 2011). Reciprocally, depletion of NFκB can also trigger DNA demethylation and gene reactivation, illustrating gene-specific epigenetic effects which may further depend on posttranslational NFκB modifications (Dong et al., 2008; X. Liu et al., 2010b; Y. Liu et al., 2011). Also, chronic exposure to chemotherapeutic agents may epigenetically reprogram cancer cell metabolism and gene expression and trigger chemoresistance (Blair et al., 2011; Kujjo et al., 2011; S. V. Sharma et al., 2010; W. Suttana et al., 2010). As such, this demonstrates that cancer-inflammation pathways and transcription factors are able to rewire epigenetic settings and amplify gene expression in an autocrine fashion (Hervouet et al., 2009; S. Liu et al., 2008).

Of special note, despite promising (pre)clinical studies with epigenetic drugs (azacytidin, suberoylanilide hydroxamic acid (SAHA)) for reactivation of silenced tumor suppressor genes in cancer treatment, one should also be precautious, as these compounds may also boost gene expression of inflammatory oncogenes such as IL6, which promote aggressive carcinogenesis, cancer stem cell proliferation, metastasis and hormone resistance (B. B. Aggarwal & Gehlot, 2009; S. Grivennikov et al., 2009; D. Iliopoulos et al., 2009; S. Maeda et al., 2009; Min et al., 2010; Naugler & Karin, 2008; W. Suttana et al., 2010; H. Wang et al., 2009; Yu et al., 2009). In line with this, knocking out DNMT1 or treatment of tumors with a global DNA hypomethylating agent was found to promote aspects of tumor progression and was accompanied by increased invasion *in vitro* and increase tumor growth *in vivo* (Eden et al., 2003; Gaudet et al., 2003; Christopher A. Hamm & Costa, 2011; C. A. Hamm et al., 2009). Furthermore, the inflammatory cytokine IL6 is able to trigger epigenetic changes of tumor suppressor genes via regulation of DNMTs (Gasche et al., 2011; Hodge et al., 2007; Hodge et al., 2005b; Peng et al., 2005; Pompeia et al., 2004), microRNAs (Braconi et al., 2010; D. Iliopoulos et al., 2009; Meng et al., 2008) and histone methyltransferases (Ezh2) (Croonquist & Van Ness, 2005). Another regulatory circuit involving NFκB, STAT3, IL6, and let7, miR-21 and miR-181b-1 triggers an epigenetic switch driving tumor progression (D. Iliopoulos et al., 2009 & 2010). Remarkably, expression of enzymes central to cellular methylation, S-adenosylmethionine synthetase and S-adenosylhomocysteine, as well levels of specific

metabolites associated with cellular methylation reactions are significantly altered during inflammation, which results in a global change in DNA/histone methylation during inflammation (Kominsky et al., 2011). This suggests that epigenetic regulators themselves and methylation of tumor suppressor genes are also susceptible to dynamic inflammatory control (Braconi et al., 2010; Hodge et al., 2005a; Hodge et al., 2001; D. Iliopoulos et al., 2009; Kawasaki et al., 2008; Mathews et al., 2009; Meng et al., 2008; Peng et al., 2005), 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 NF $\kappa$ B-dependent histone demethylase JMJD3 which determines cell fate and transdifferentiation of tumor-associated macrophages (De Santa et al., 2007; K. C. Kim et al., 2009b). 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 (D. Iliopoulos et al., 2009; S. V. Sharma et al., 2010). However, also tumor stromal components (which include bone-marrow-derived cells, tumor-associated macrophages) are a target of epigenetic events (De Santa et al., 2007; Dijsselbloem et al., 2007; Messi et al., 2003). 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 $_2$ O $_2$  and Reactive Nitrogen Species (RNS) such as  $\bullet$ NO and  $\bullet$ NO $_2$  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 ROS and RNS intermediates, indirectly also modulate activity of epigenetic machinery which finally will affect chromatin dynamics and DNA (hydroxyl)methylation in tumor-associated immune cells (Brewer, 2010; Carta et al., 2009; Forneris et al., 2008; Franco et al., 2008; Illi et al., 2009).

## 6. Nutri-epigenomics: Lifelong remodelling of our epigenomes

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 (Aguilera et al., 2010; Burdge & Lillycrop, 2010; Cooney, 2006; Gallou-Kabani et al., 2007; Godfrey et al., 2010; Weaver, 2009; Youngson & Whitelaw, 2008). This has led to the hypothesis of "fetal programming" and new term "developmental origin of health and disease" (DOHaD): common disorders, such as cancer, obesity, cardiovascular disease (CVD), diabetes, hypertension, asthma and even schizophrenia, take root in early nutrition during gestation and continues during lactation (Anway et al., 2005; Anway & Skinner, 2006; Barker & Martyn, 1992; Burdge & Lillycrop, 2010; Chmurzynska, 2010; Gluckman et al., 2008; Hochberg et al., 2011; Jackson et al., 2010; Jirtle & Skinner, 2007). Similarly, there is increasing evidence in animals that nutritional intervention (caloric, iron and protein restriction, polyphenol-, folate-, micronutrient-, fat- or carbohydrate-rich diet) and maternal diabetes occurring during pregnancy and the lactation period, affects health in following

generation(s) (Dolinoy & Jirtle, 2008; Jirtle & Skinner, 2007; Kirk et al., 2008; Waterland, 2009; Waterland & Jirtle, 2004; Waterland et al., 2008; Youngson & Whitelaw, 2008). 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 (Aguilera et al., 2010; Bell & Spector, 2011; Burdge & Lillycrop, 2010; Cooney, 2006; Gallou-Kabani et al., 2007; Godfrey et al., 2010; Kaminsky et al., 2009; Petronis, 2006; Weaver, 2009; Youngson & Whitelaw, 2008). Thus, lifetime shapes the multitude of epigenomes not only within, but also across generations (Anway & Skinner, 2006; Burdge & Lillycrop, 2010; Chong et al., 2007; Godfrey et al., 2010; Hochberg et al., 2011; Skinner et al., 2011; Youngson & Whitelaw, 2008). 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. This in turn protected them against diabetes, obesity and cancer across multiple generations (Dolinoy & Jirtle, 2008; Dolinoy et al., 2006; Waterland, 2009). Furthermore, maternal nutrient supplementation with soy polyphenols was found to counteract xenobiotic-induced DNA hypomethylation in early development (Dolinoy et al., 2007; Dolinoy & Jirtle, 2008; Dolinoy et al., 2006; Jirtle & Skinner, 2007; Kujjo et al., 2011; Skinner et al., 2011).

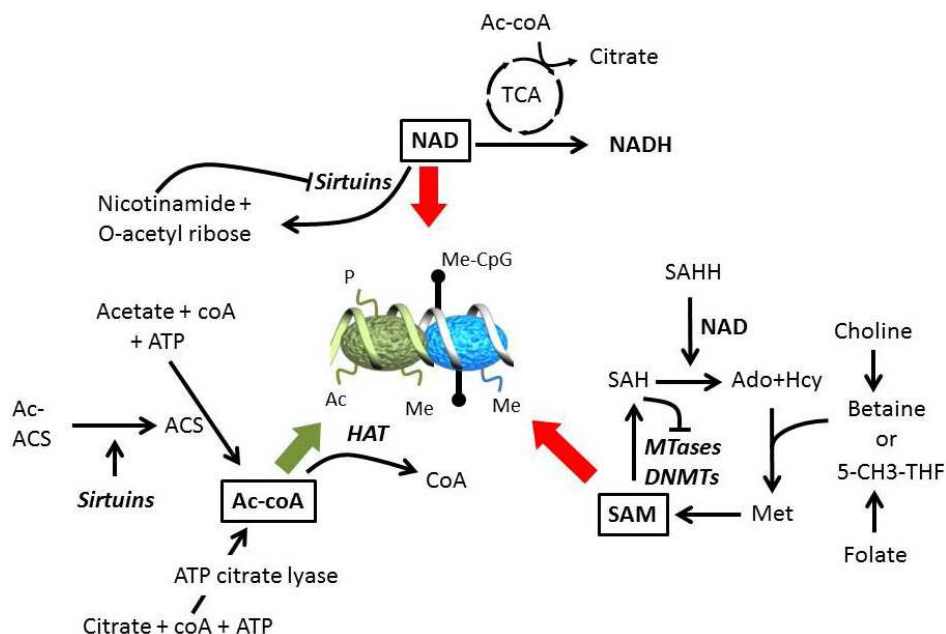
Recently, evidence emerged that also timing (preconception, pregnancy, lactation, neonatal life, early life, pre-/post-menopause, puberty) of various dietary exposures may be vitally important in determining health beneficial effects, as epigenetic plasticity changes continually from conception to death (Burdge et al., 2009; Faulk & Dolinoy, 2011). Studies of human populations following famine have suggested that pathologies in later life are dependent on the critical timing of nutritional insult during pregnancy (Lumey & Stein, 2009; Painter et al., 2008; Roseboom et al., 2006). 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 (Aguilera et al., 2010). 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 (Christensen et al., 2009; Fraga et al., 2005). 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% (Hajkova et al., 2008; Surani et al., 2004). Remarkably, recent evidence suggests that DNA methylation is rather converted into hydroxymethylation than erased (Ficz et al., 2011; Iqbal et al., 2011; Wossidlo et al., 2010; Wossidlo et al., 2011). Alternatively, it can not be excluded that transgenerationally inherited nutritional effects may also depend on polycomb proteins (Blewitt et al., 2006; Bracken & Helin, 2009; Chong et al., 2007; Youngson & Whitelaw, 2008), miRNA profiles (Guil & Esteller, 2009; Y. Li et al., 2010) or epigenetic capacitor properties of hsp proteins present in the fertilized embryo (Ruden et al., 2005a; Ruden et al., 2005b; Sollars et al., 2003).



## 7. Epigenetic targets of bioactive dietary components for cancer prevention and therapy

A next challenge will be to determine which adverse epigenomic marks in cancer-inflammation are reversible or can be prevented by specific diets, natural phytochemicals or lifestyle changes (Burdge & Lillycrop, 2010; Burdge et al., 2009; Godfrey et al., 2010; Kirk et al., 2008). Numerous botanical species and plant parts contain a diverse array of polyphenolic phytochemicals which exert cancer-chemopreventive effects in man by its anti-inflammatory, anti-oxidant, phytohormonal, homeostatic effects (hormesis) in immune cells and/or cancer (stem)cells (Bickford et al., 2006; Blanpain & Fuchs, 2009; Crea et al., 2009; Dijsselbloem et al., 2004; Kawasaki et al., 2008; Shytle et al., 2007; Surh, 2003; Zhou et al., 2008). Upon re-exploration of its biological activities, various nutritional natural compounds (including epigallocatechingallate, resveratrol, genistein, curcumin, isothiocyanates, withanolides, ...) were found to interfere with enzymatic activity of DNMT, Class I, II, IV HDAC, HAT and Class III HDAC sirtuins (SIRT) which modulate cancer-inflammation ((Arasaradnam et al., 2008; Burdge & Lillycrop, 2010; Delage & Dashwood, 2008; Fang et al., 2007; Folmer et al., 2010; Hauser & Jung, 2008; Jackson et al., 2010; Kirk et al., 2008; Kontogiorgis et al., 2010; Link et al., 2010; Suzuki & Miyata, 2006; Szarc vel Szic et al., 2010; Vaquero & Reinberg, 2009), and references included). 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 dinucleotide (NAD<sup>+</sup>)-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 (Folmer et al., 2010). 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). 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). Specific epigenetic effects of natural phytochemicals may be the result of a superposition of combined concentration-dependent actions of the compound as a nuclear hormone receptor ligand and/or modulator of histone-modifying enzymes and DNMTs (Darbre & Charles, 2010; Denison & Nagy, 2003; Kuniyasu, 2008; Mai et al., 2008; Newbold et al., 2009) which may target chromatin dynamics of specific gene clusters. Although 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 (Manach & Donovan, 2004; Manach et al., 2005a; Manach et al., 2004; Manach et al., 2005b; Williamson & Manach, 2005). Furthermore, it should be evaluated which epigenetic changes are stable over time. Interestingly, even transient exposure to a specific dietary component can induce

long-lasting epigenetic changes in the promoter of the NF $\kappa$ B subunit p65, which acts as a master switch in cancer-inflammation (El-Osta et al., 2008). Alternatively, compounds may chemically interfere with histone mark interacting effector domains (such as chromo-, bromo- or tudor domains) (Seet et al., 2006; Wigle et al.; Zheng et al., 2008). Though, upon performing *in vitro* compound screenings in cofactor activity assays based on peptide-protein interactions, one should be careful with interpretation as peptide interactions may not always represent true targets *in vivo* (Altucci & Minucci, 2009; Pacholec et al., 2010).



NAD, acetyl-coenzyme A (Acetyl-coA) and S-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 (SIRT), which uses NAD as one of the substrates. Sirtuins are also important for maintaining the activity of the acetyl-coA acetyltransferases. Ac-coA is synthesized by acetyl-coA-synthetase and ATP-citrate lyase that use acetate and citrate as the precursor, respectively. Citrate is an intermediate/product of the TCA cycle. SAM is the methyl donor for DNA, RNA, histones and non-histone protein methylation. SAH generated in each round of methylation reaction is a potent inhibitor of methyltransferases and has to be cleared by SAH hydrolase. 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 folic acid. Metabolism of phospholipids and folic 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: Ac-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; SAH, S-adenosyl homocysteine; TCA tricarboxylic cycle; THF tetrahydrofolate.

Fig. 5. Global shifts in cancer epigenome regulation depend on metabolic shifts in cofactors for epigenetic enzymes (adapted from Luo et al. 2009)

From another perspective, chemopreventive phytochemicals may indirectly modulate chromatin dynamics and epigenetic effects upon interference with global cancer metabolism. As such, epigenetic changes may follow biochemical metabolism of dietary factors, which can deplete cellular pools of acetyl-CoA, NAD<sup>+</sup> and methyl donors, resulting in unbalanced DNA methylation and/or protein acetylation or methylation (Imai & Guarente, 2010; Ladurner, 2009; Vaquero & Reinberg, 2009) (Figure 1&5). For example, flavanol-rich diets interfere with the methyl donor metabolism and the available pool of S-adenosylmethionine, resulting in changes in DNA methylation (Bistulfi et al., 2010; N. C. Chen et al., 2010; Ghoshal et al., 2006; J. M. Kim et al., 2009a; Ulrich et al., 2008) and histone methylation, which is also affected by alterations in SAM/SAH ratios (Pogribny et al., 2007; P. Sharma et al., 2006). Furthermore, 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 (D. H. Lee et al., 2009). Diets or nutritional compounds which affect energy metabolism or mitochondrial respiration can have global epigenetic effects upon changes in NAD<sup>+</sup> availability and SIRT activity (Whittle et al., 2007). 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 (Imai & Guarente, 2010). Along the same line, flavanol-rich diets which interfere with the methyl donor metabolism and the available pool of S-adenosylmethionine will result in (Global) changes in DNA and histone methylation (Bistulfi et al., 2010; Ghoshal et al., 2006; J. M. Kim et al., 2009a; Pogribny et al., 2007; P. Sharma et al., 2006; Ulrich et al., 2008). As such, specific dietary classes of functional food maybe designed as therapeutic epigenetic modulators in cancer-inflammation.

## 8. Conclusion & future perspectives

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 contribute to many cancer types. 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 cancer. Much attention is currently focusing on modulating DNA hyper/hypomethylation of key inflammatory genes by dietary factors as an effective approach to cure or protect against cancer-inflammation (Burdge & Lillycrop, 2010; Delage & Dashwood, 2008; Fang et al., 2007; Folmer et al., 2010; Hauser & Jung, 2008; Jackson et al., 2010; Kirk et al., 2008; Kontogiorgis et al., 2010; Link et al., 2010; Suzuki & Miyata, 2006; Vaquero & Reinberg, 2009). 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 tumor microenvironment (Bremner & Heinrich, 2002; Deorukhkar et al., 2007; Karin et al., 2004; Khanna et al., 2007; Paul et al.,

2006; Rios et al., 2009; Surh, 2003). 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 environmental 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 (Burdge & Lillycrop, 2010; Dijsselbloem et al., 2007; Manach et al., 2005b; N. Ndlovu et al., 2009; Vanden Berghe et al., 2006a; Williamson & Manach, 2005). There is some concern that epigenetic therapy with dietary inhibitors of DNMT, HDAC, histone (de)methylases in longterm treatment setups may suffer from lack of specificity (Altucci & Minucci, 2009; Mai et al., 2008; Zheng et al., 2008). As such, the possible alternative is to combine nonselective epigenetic therapies with more targeted approaches (Hervouet et al., 2009). 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 (Biddie et al., 2010; Di Croce et al., 2002; Fiskus et al., 2009; Hervouet et al., 2009; Perissi et al., 2010). 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 (Delage & Dashwood, 2008). 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 (De Santa et al., 2010; Guil & Esteller, 2009; Gupta et al., 2010; Parasramka et al., 2011; Tsai et al., 2010). In conclusion, cancer-inflammation 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 for chemoprevention. Medical benefits of dietary compounds as epigenetic modulators, especially with respect to their chronic use as nutraceutical agents in cancer chemoprevention, will rely on our further understanding of their epigenetic effects during embryogenesis, early life, aging, carcinogenesis as well as through different generations.

## 9. Acknowledgements

This research is partially financial supported by FP7 grant FLAVIOLA ([www.flaviola.org](http://www.flaviola.org)), Research Grant from the Multiple Myeloma Research Foundation (MMRF) and an NOI grant (UA).

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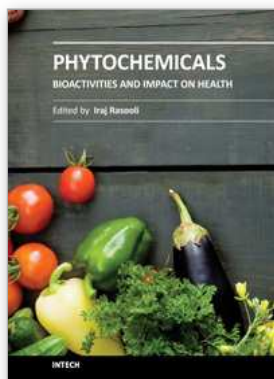
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## **Phytochemicals - Bioactivities and Impact on Health**

Edited by Prof. Iraj Rasooli

ISBN 978-953-307-424-5

Hard cover, 388 pages

**Publisher** InTech

**Published online** 22, December, 2011

**Published in print edition** December, 2011

Among the thousands of naturally occurring constituents so far identified in plants and exhibiting a long history of safe use, there are none that pose - or reasonably might be expected to pose - a significant risk to human health at current low levels of intake when used as flavoring substances. Due to their natural origin, environmental and genetic factors will influence the chemical composition of the plant essential oils. Factors such as species and subspecies, geographical location, harvest time, plant part used and method of isolation all affect chemical composition of the crude material separated from the plant. The screening of plant extracts and natural products for antioxidative and antimicrobial activity has revealed the potential of higher plants as a source of new agents, to serve the processing of natural products.

### **How to reference**

In order to correctly reference this scholarly work, feel free to copy and paste the following:

Katarzyna Szarc vel Szic, Ajay Palagani, Behrouz Hassannia, Linde Sabbe, Karen Heyninck, Guy Haegeman and Wim Vanden Berghe (2011). Phytochemicals and Cancer Chemoprevention: Epigenetic Friends or Foe?, *Phytochemicals - Bioactivities and Impact on Health*, Prof. Iraj Rasooli (Ed.), ISBN: 978-953-307-424-5, InTech, Available from: <http://www.intechopen.com/books/phytochemicals-bioactivities-and-impact-on-health/phytochemicals-and-cancer-chemoprevention-epigenetic-friends-or-foe->

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