7

Phytochemicals and Cancer Chemoprevention: Epigenetic Friends or Foe?

Katarzyna Szarc vel Szic[1], Ajay Palagani[1,2], Behrouz Hassannia[2], Linde Sabbe[2], Karen Heyninck[2], Guy Haegeman[2] and Wim Vanden Berghe[1,2]
[1]Laboratory of Protein Science, Proteomics and Epigenetic Signaling (PPES), Department of Biomedical Sciences, University Antwerp, Campus Drie Eiken, Wilrijk,
[2]Laboratory of Eukaryotic Gene Expression and Signal Transduction (LEGEST), Department of Physiology, Ghent University, Gent,
Belgium

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+, S-adenosylmethionine, see Figure 1) of which the concentrations are tighly 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; Dalgliesh 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).

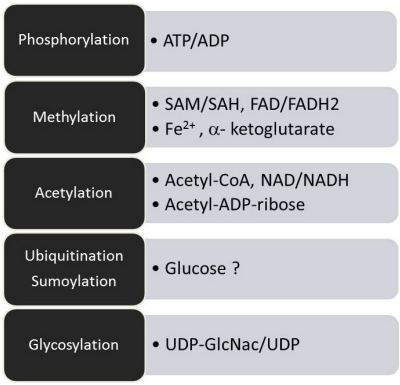


Fig. 1. Coupling of cancer metabolism, diet and epigenetics

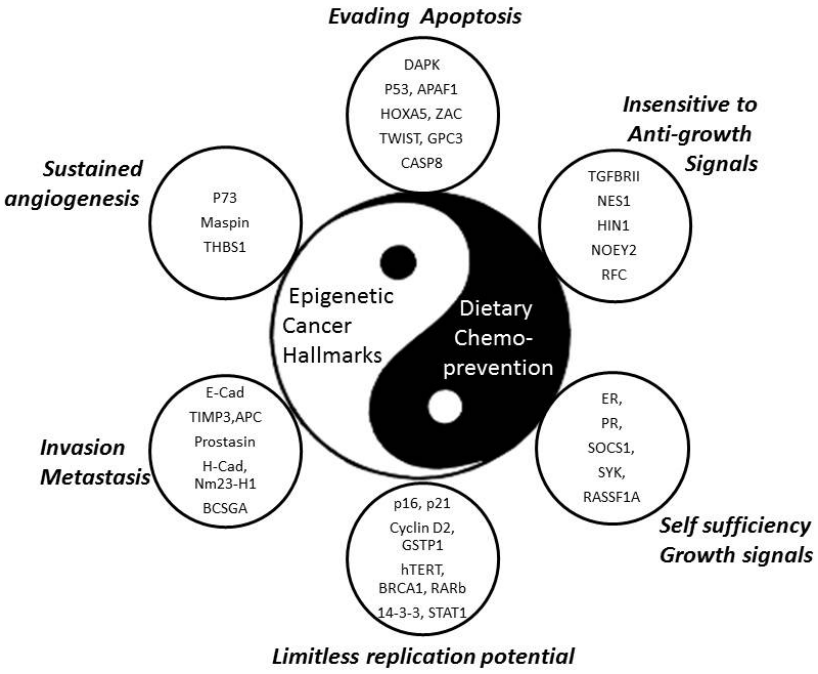


Fig. 2. Dietary reversal of epigetic changes in cancer cells

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- γ (PPAR γ), 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 Szic 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,

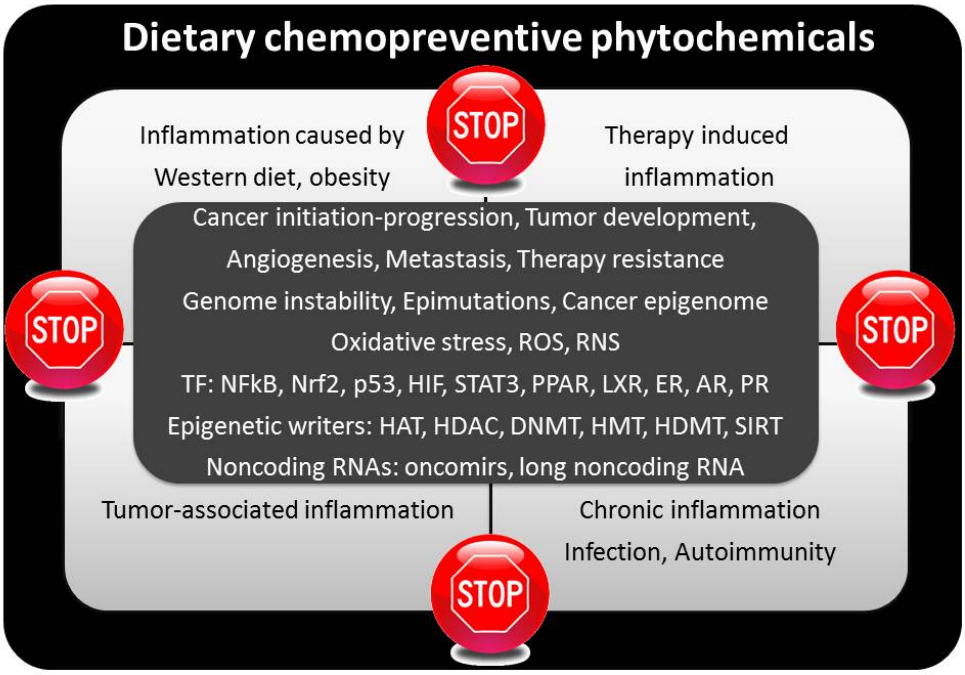


Fig. 3. Dietary chemoprevention of cancer-inflammation

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 expresion 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 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 (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 combinatory 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 killling, thereby evading eradication. For example, cancer cells may paralyze infiltrating CTLs and NK cells, by secreting TGFβ 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 & Horng, 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.

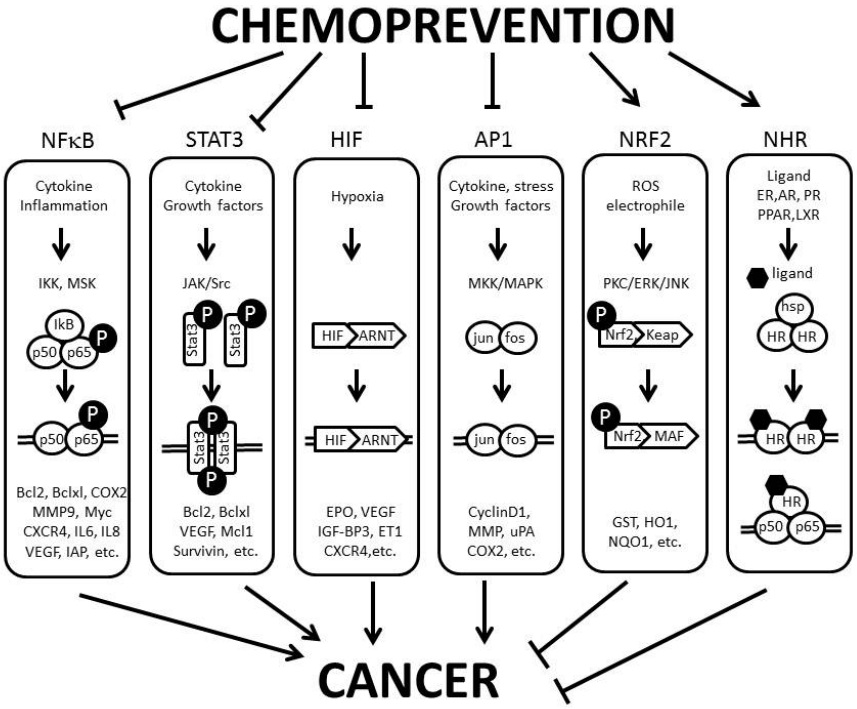
4.1 Cell specific mechanisms in the tumor microenvironment

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, NFκB 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). NFκB 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 NFκB pathway is regulated by many other pathways, i.e. EGFR/Her2-PI3K-Akt/IKKα, RSK2, MSK1, TP53 PTEN, Akt-mTOR, Ras, Raf, Wnt-catenin, hypoxia, oxidative stress (Chaturvedi et al., 2011). In nonstimulated cells, 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 transcription factors, 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). 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 (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 NFκB 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 NFκB/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 NFκB found in several human cancer cell lines, including lymphomas and carcinomas of the breast, prostate, lung, colon, pancreas, head and neck and oesophagus, activated NFκB 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 NFκB or p53 mutations could direct constitutive NFκB activation in cancer cell lines and patient samples (Dey et al., 2008; Dijsselbloem et al. 2007; Weisz et al., 2007). Therefore, inhibition of NFκB 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 NFκB-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 NFκB subunits and their respective posttranslational modifications, and by combinatorial interactions between NFκB 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- γ (PPAR γ), 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 NFκB, 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)β preferentially activates SWI/SNF-dependent non-CpG-island promoters. At the level of CpG methylation, changes in DNA methylation of IKK, IκB and RelB promoters (G. Maeda et al., 2007; O'Gorman et al., 2010; Puto & Reed, 2008) affect gene induction properties upon re-exposure to a 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 phosphacetylation 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, NFkB 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 NFκB-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 •O2, •OH, H2O2 and Reactive Nitrogen Species (RNS) such as •NO and •NO2 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

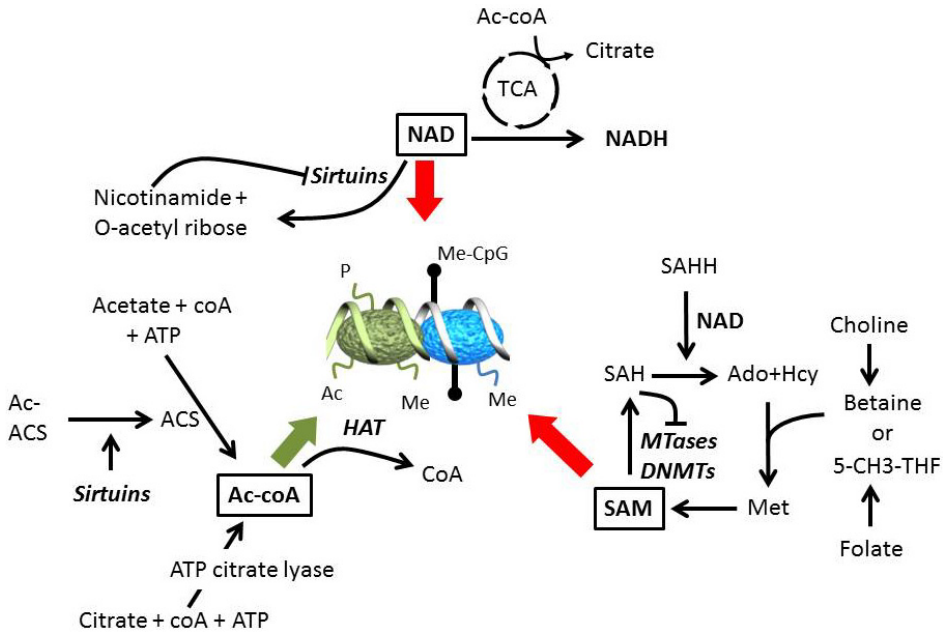
generation(s) (Dolinoy & Jirtle, 2008; Jirtle & Skinner, 2007; Kirk et al., 2008; Waterland, 2009; Waterland & Jirtle, 2004; Waterland et al., 2008; Youngson & Whitelaw, 2008). The various non-Mendelian features of metabolic disease, cancer or chronic inflammatory disorders, clinical differences between 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 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 (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 NFκB 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 homocystein 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 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 (Imai & Guarente, 2010; Ladurner, 2009; Vaquero & Reinberg, 2009) (Figure 1&5). For example, flavanol-rich diets interfere with the methyldonor 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+ 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 methyldonor 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-inflammaton 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), Research Grant from the Multiple Myeloma Research Foundation (MMRF) and an NOI grant (UA).

10. References

(2008) Moving AHEAD with an international human epigenome project. Nature 454: 711-715

Aaltonen, T.; Adelman, J.; Akimoto, T.; Albrow, M. G.; Alvarez Gonzalez, B.; Amerio, S.; Amidei, D.; Anastassov, A.; Annovi, A.; Antos, J.; Aoki, M.; Apollinari, G.; Apresyan, A.; Arisawa, T.; Artikov, A.; Ashmanskas, W.; Attal, A.; Aurisano, A.; Azfar, F.; Azzi-Bacchetta, P. et al (2008) Cross-section-constrained top-quark mass measurement from dilepton events at the Tevatron. Physical Review Letters 100: 062005

Aggarwal, B. B. (2009) Inflammation, a silent killer in cancer is not so silent! Curr Opin Pharmacol 9: 347-350

Aggarwal, B. B. (2010) Targeting Inflammation-Induced Obesity and Metabolic Diseases by Curcumin and Other Nutraceuticals. Annual Review of Nutrition 30: 173-199

Aggarwal, B. B. & Gehlot, P. (2009) Inflammation and cancer: how friendly is the relationship for cancer patients? Curr Opin Pharmacol 9: 351-369

Aggarwal, B. B.; Prasad, S.; Reuter, S.; Kannappan, R.; Yadev, V. R.; Park, B.; Kim, J. H.; Gupta, S. C.; Phromnoi, K.; Sundaram, C.; Chaturvedi, M. M. & Sung, B. (2011) Identification of Novel Anti-inflammatory Agents from Ayurvedic Medicine for Prevention of Chronic Diseases: "Reverse Pharmacology" and "Bedside to Bench" Approach. Curr Drug Targets

Aguilera, O.; Fernandez, A. F.; Munoz, A. & Fraga, M. F. (2010) Epigenetics and environment: a complex relationship. J Appl Physiol 109: 243-251

Altucci, L. & Minucci, S. (2009) Epigenetic therapies in haematological malignancies: searching for true targets. Eur J Cancer 45: 1137-1145

Anand, P.; Kunnumakkara, A. B.; Sundaram, C.; Harikumar, K. B.; Tharakan, S. T.; Lai, O. S.; Sung, B. & Aggarwal, B. B. (2008) Cancer is a preventable disease that requires major lifestyle changes. PharmRes 25: 2097-2116

Anway, M. D.; Cupp, A. S.; Uzumcu, M. & Skinner, M. K. (2005) Epigenetic transgenerational actions of endocrine disruptors and male fertility. Science 308: 1466-1469

Anway, M. D. & Skinner, M. K. (2006) Epigenetic transgenerational actions of endocrine disruptors. Endocrinology 147: S43-49

Arasaradnam, R. P.; Commane, D. M.; Bradburn, D. & Mathers, J. C. (2008) A review of dietary factors and its influence on DNA methylation in colorectal carcinogenesis. Epigenetics 3: 193-198

Arkan, M. C.; Hevener, A. L.; Greten, F. R.; Maeda, S.; Li, Z. W.; Long, J. M.; Wynshaw-Boris, A.; Poli, G.; Olefsky, J. & Karin, M. (2005) IKK-beta links inflammation to obesity-induced insulin resistance. Nat Med 11: 191-198

Armenante, F.; Merola, M.; Furia, A. & Palmieri, M. (1999) Repression of the IL-6 gene is associated with hypermethylation. Biochem Biophys Res Commun 258: 644-647

Ashall, L.; Horton, C. A.; Nelson, D. E.; Paszek, P.; Harper, C. V.; Sillitoe, K.; Ryan, S.; Spiller, D. G.; Unitt, J. F.; Broomhead, D. S.; Kell, D. B.; Rand, D. A.; See, V. & White, M. R. (2009) Pulsatile stimulation determines timing and specificity of NF-kappaB-dependent transcription. Science 324: 242-246

Backdahl, L.; Bushell, A. & Beck, S. (2009) Inflammatory signalling as mediator of epigenetic modulation in tissue-specific chronic inflammation. Int J Biochem Cell Biol 41: 176-184

Balkwill, F.; Charles, K. A. & Mantovani, A. (2005) Smoldering and polarized inflammation in the initiation and promotion of malignant disease. Cancer Cell 7: 211-217

Balkwill, F. & Mantovani, A. (2010) Cancer and inflammation: implications for pharmacology and therapeutics. Clin Pharmacol Ther 87: 401-406

Barker, D. J. & Martyn, C. N. (1992) The maternal and fetal origins of cardiovascular disease. Journal of Epidemiology and Community Health 46: 8-11

Baud, V. & Karin, M. (2009) Is NF-kappaB a good target for cancer therapy? Hopes and pitfalls. Nat Rev Drug Discov 8: 33-40

Bell, J. T. & Spector, T. D. (2011) A twin approach to unraveling epigenetics. Trends Genet 27: 116-125

Bellet, M. M. & Sassone-Corsi, P. (2010) Mammalian circadian clock and metabolism - the epigenetic link. J Cell Sci 123: 3837-3848

Berdasco, M. & Esteller, M. (2010) Aberrant Epigenetic Landscape in Cancer: How Cellular Identity Goes Awry. Developmental Cell 19: 698-711

Bickford, P. C.; Tan, J.; Shytle, R. D.; Sanberg, C. D.; El-Badri, N. & Sanberg, P. R. (2006) Nutraceuticals synergistically promote proliferation of human stem cells. Stem Cells Dev 15: 118-123

Bickmore, W. A.; Tolhuis, B.; Blom, M.; Kerkhoven, R. M.; Pagie, L.; Teunissen, H.; Nieuwland, M.; Simonis, M.; de Laat, W.; van Lohuizen, M. & van Steensel, B. (2011) Interactions among Polycomb Domains Are Guided by Chromosome Architecture. PLoS Genetics 7: e1001343

Biddie, S. C.; John, S. & Hager, G. L. (2010) Genome-wide mechanisms of nuclear receptor action. Trends Endocrinol Metab 21: 3-9

Bingham, S. & Riboli, E. (2004) Diet and cancer--the European Prospective Investigation into Cancer and Nutrition. Nat Rev Cancer 4: 206-215

Bird, A. (2002) DNA methylation patterns and epigenetic memory. Genes Dev 16: 6-21

Birney, E.; Stamatoyannopoulos, J. A.; Dutta, A.; Guigo, R.; Gingeras, T. R.; Margulies, E. H.; Weng, Z.; Snyder, M.; Dermitzakis, E. T.; Thurman, R. E.; Kuehn, M. S.; Taylor, C. M.; Neph, S.; Koch, C. M.; Asthana, S.; Malhotra, A.; Adzhubei, I.; Greenbaum, J. A.; Andrews, R. M.; Flicek, P. et al (2007) Identification and analysis of functional elements in 1% of the human genome by the ENCODE pilot project. Nature 447: 799-816

Bistulfi, G.; Vandette, E.; Matsui, S. & Smiraglia, D. J. (2010) Mild folate deficiency induces genetic and epigenetic instability and phenotype changes in prostate cancer cells. BMCBiol 8: 6

Blair, L. P.; Cao, J.; Zou, M. R.; Sayegh, J. & Yan, Q. (2011) Epigenetic Regulation by Lysine Demethylase 5 (KDM5) Enzymes in Cancer. Cancers (Basel) 3: 1383-1404

Blanpain, C. & Fuchs, E. (2009) Epidermal homeostasis: a balancing act of stem cells in the skin. Nat Rev Mol Cell Biol 10: 207-217

Blewitt, M. E.; Vickaryous, N. K.; Paldi, A.; Koseki, H. & Whitelaw, E. (2006) Dynamic Reprogramming of DNA Methylation at an Epigenetically Sensitive Allele in Mice. PLoS Genet 2: e49

Boeke, J.; Regnard, C.; Cai, W.; Johansen, J.; Johansen, K. M.; Becker, P. B. & Imhof, A. (2010) Phosphorylation of SU(VAR)3-9 by the chromosomal kinase JIL-1. PLoS ONE 5: e10042

Boffetta, P.; Couto, E.; Wichmann, J.; Ferrari, P.; Trichopoulos, D.; Bueno-de-Mesquita, H. B.; van Duijnhoven, F. J.; Buchner, F. L.; Key, T.; Boeing, H.; Nothlings, U.; Linseisen, J.; Gonzalez, C. A.; Overvad, K.; Nielsen, M. R.; Tjonneland, A.; Olsen, A.; Clavel-Chapelon, F.; Boutron-Ruault, M. C.; Morois, S. et al (2010) Fruit and vegetable intake and overall cancer risk in the European Prospective Investigation into Cancer and Nutrition (EPIC). Journal of the National Cancer Institute 102: 529-537

Bonuccelli, G.; Tsirigos, A.; Whitaker-Menezes, D.; Pavlides, S.; Pestell, R. G.; Chiavarina, B.; Frank, P. G.; Flomenberg, N.; Howell, A.; Martinez-Outschoorn, U. E.; Sotgia, F. & Lisanti, M. P. (2010) Ketones and lactate "fuel" tumor growth and metastasis:

Evidence that epithelial cancer cells use oxidative mitochondrial metabolism. Cell Cycle 9: 3506-3514

Bracken, A. P. & Helin, K. (2009) Polycomb group proteins: navigators of lineage pathways led astray in cancer. Nat Rev Cancer 9: 773-784

Braconi, C.; Huang, N. & Patel, T. (2010) MicroRNA-dependent regulation of DNA methyltransferase-1 and tumor suppressor gene expression by interleukin-6 in human malignant cholangiocytes. Hepatology 51: 881-890

Bremner, P. & Heinrich, M. (2002) Natural products as targeted modulators of the nuclear factor-kappaB pathway. J Pharm Pharmacol 54: 453-472

Brenner, C.; Deplus, R.; Didelot, C.; Loriot, A.; Vire, E.; De Smet, C.; Gutierrez, A.; Danovi, D.; Bernard, D.; Boon, T.; Pelicci, P. G.; Amati, B.; Kouzarides, T.; de Launoit, Y.; Di Croce, L. & Fuks, F. (2005) Myc represses transcription through recruitment of DNA methyltransferase corepressor. EMBO J 24: 336-346

Brewer, G. J. (2010) Epigenetic oxidative redox shift (EORS) theory of aging unifies the free radical and insulin signaling theories. Experimental Gerontology 45: 173-179

Brower, V. (2011) Epigenetics: Unravelling the cancer code. Nature 471: S12-13

Burdge, G. C. & Lillycrop, K. A. (2010) Nutrition, Epigenetics, and Developmental Plasticity: Implications for Understanding Human Diseas. Annual Review of Nutrition

Burdge, G. C.; Lillycrop, K. A. & Jackson, A. A. (2009) Nutrition in early life, and risk of cancer and metabolic disease: alternative endings in an epigenetic tale? British Journal of Nutrition 101: 619-630

Carta, S.; Castellani, P.; Delfino, L.; Tassi, S.; Vene, R. & Rubartelli, A. (2009) DAMPs and inflammatory processes: the role of redox in the different outcomes. J Leukoc Biol 86: 549-555

Chang, J.; Zhang, B.; Heath, H.; Galjart, N.; Wang, X. & Milbrandt, J. (2010) Nicotinamide adenine dinucleotide (NAD)-regulated DNA methylation alters CCCTC-binding factor (CTCF)/cohesin binding and transcription at the BDNF locus. Proceedings of the National Academy of Sciences of the United States of America 107: 21836-21841

Chaturvedi, M. M.; Sung, B.; Yadav, V. R.; Kannappan, R. & Aggarwal, B. B. (2011) NF-kappaB addiction and its role in cancer: 'one size does not fit all'. Oncogene 30: 1615-1630

Chen, L. F. & Greene, W. C. (2004) Shaping the nuclear action of NF-kappaB. Nat Rev Mol Cell Biol 5: 392-401

Chen, N. C.; Yang, F.; Capecci, L. M.; Gu, Z.; Schafer, A. I.; Durante, W.; Yang, X. F. & Wang, H. (2010) Regulation of homocysteine metabolism and methylation in human and mouse tissues. FASEB Journal

Chi, P.; Allis, C. D. & Wang, G. G. (2010) Covalent histone modifications--miswritten, misinterpreted and mis-erased in human cancers. Nat Rev Cancer 10: 457-469

Chmurzynska, A. (2010) Fetal programming: link between early nutrition, DNA methylation, and complex diseases. Nutrition Reviews 68: 87-98

Chodavarapu, R. K.; Feng, S.; Bernatavichute, Y. V.; Chen, P. Y.; Stroud, H.; Yu, Y.; Hetzel, J. A.; Kuo, F.; Kim, J.; Cokus, S. J.; Casero, D.; Bernal, M.; Huijser, P.; Clark, A. T.; Kramer, U.; Merchant, S. S.; Zhang, X.; Jacobsen, S. E. & Pellegrini, M. (2010) Relationship between nucleosome positioning and DNA methylation. Nature 466: 388-392

Chong, S.; Youngson, N. A. & Whitelaw, E. (2007) Heritable germline epimutation is not the same as transgenerational epigenetic inheritance. Nature Genetics 39: 574-575; author reply 575-576

Christensen, B. C.; Houseman, E. A.; Marsit, C. J.; Zheng, S.; Wrensch, M. R.; Wiemels, J. L.; Nelson, H. H.; Karagas, M. R.; Padbury, J. F.; Bueno, R.; Sugarbaker, D. J.; Yeh, R. F.; Wiencke, J. K. & Kelsey, K. T. (2009) Aging and environmental exposures alter tissue-specific DNA methylation dependent upon CpG island context. PLoS Genet 5: e1000602

Cooney, C. A. (2006) Germ cells carry the epigenetic benefits of grandmother's diet. Proceedings of the National Academy of Sciences of the United States of America 103: 17071-17072

Cosgrove, M. S. & Wolberger, C. (2005) How does the histone code work? Biochemistry and Cell Biology 83: 468-476

Crea, F.; Mathews, L. A.; Farrar, W. L. & Hurt, E. M. (2009) Targeting prostate cancer stem cells. Anticancer Agents Med Chem 9: 1105-1113

Croonquist, P. A. & Van Ness, B. (2005) The polycomb group protein enhancer of zeste homolog 2 (EZH 2) is an oncogene that influences myeloma cell growth and the mutant ras phenotype. Oncogene 24: 6269-6280

Dalgliesh, G. L.; Furge, K.; Greenman, C.; Chen, L.; Bignell, G.; Butler, A.; Davies, H.; Edkins, S.; Hardy, C.; Latimer, C.; Teague, J.; Andrews, J.; Barthorpe, S.; Beare, D.; Buck, G.; Campbell, P. J.; Forbes, S.; Jia, M.; Jones, D.; Knott, H. et al (2010) Systematic sequencing of renal carcinoma reveals inactivation of histone modifying genes. Nature 463: 360-363

Dandrea, M.; Donadelli, M.; Costanzo, C.; Scarpa, A. & Palmieri, M. (2009) MeCP2/H3meK9 are involved in IL-6 gene silencing in pancreatic adenocarcinoma cell lines. Nucleic Acids Res 37: 6681-6690

Darbre, P. D. & Charles, A. K. (2010) Environmental oestrogens and breast cancer: evidence for combined involvement of dietary, household and cosmetic xenoestrogens. Anticancer Res 30: 815-827

Dashwood, R. H. & Ho, E. (2007) Dietary histone deacetylase inhibitors: from cells to mice to man. Semin Cancer Biol 17: 363-369

Dashwood, R. H.; Myzak, M. C. & Ho, E. (2006) Dietary HDAC inhibitors: time to rethink weak ligands in cancer chemoprevention? Carcinogenesis 27: 344-349

Davalos, V. & Esteller, M. (2010) MicroRNAs and cancer epigenetics: a macrorevolution. Curr Opin Oncol 22: 35-45

Dawson, M. A.; Bannister, A. J.; Göttgens, B.; Foster, S. D.; Bartke, T.; Green, A. R. & Kouzarides, T. (2009) JAK2 phosphorylates histone H3Y41 and excludes HP1α from chromatin. Nature 461: 819-822

De Santa, F.; Barozzi, I.; Mietton, F.; Ghisletti, S.; Polletti, S.; Tusi, B. K.; Muller, H.; Ragoussis, J.; Wei, C. L. & Natoli, G. (2010) A large fraction of extragenic RNA pol II transcription sites overlap enhancers. PLoS Biology 8: e1000384

De Santa, F.; Totaro, M. G.; Prosperini, E.; Notarbartolo, S.; Testa, G. & Natoli, G. (2007) The histone H3 lysine-27 demethylase Jmjd3 links inflammation to inhibition of polycomb-mediated gene silencing. Cell 130: 1083-1094

Delage, B. & Dashwood, R. H. (2008) Dietary manipulation of histone structure and function. Annu Rev Nutr 28: 347-366

Delhommeau, F.; Dupont, S.; Della Valle, V.; James, C.; Trannoy, S.; Masse, A.; Kosmider, O.; Le Couedic, J. P.; Robert, F.; Alberdi, A.; Lecluse, Y.; Plo, I.; Dreyfus, F. J.; Marzac, C.; Casadevall, N.; Lacombe, C.; Romana, S. P.; Dessen, P.; Soulier, J.; Viguie, F. et al (2009) Mutation in TET2 in myeloid cancers. N Engl J Med 360: 2289-2301

Denis, H.; Ndlovu, M. N. & Fuks, F. (2011) Regulation of mammalian DNA methyltransferases: a route to new mechanisms. EMBO reports 12: 647-656

Denison, M. S. & Nagy, S. R. (2003) Activation of the aryl hydrocarbon receptor by structurally diverse exogenous and endogenous chemicals. Annual review of pharmacology and toxicology 43: 309-334

Deocaris, C. C.; Widodo, N.; Wadhwa, R. & Kaul, S. C. (2008) Merger of ayurveda and tissue culture-based functional genomics: inspirations from systems biology. J Transl Med 6: 14

Deorukhkar, A.; Krishnan, S.; Sethi, G. & Aggarwal, B. B. (2007) Back to basics: how natural products can provide the basis for new therapeutics. Expert Opin Investig Drugs 16: 1753-1773

Dey, A.; Tergaonkar, V. & Lane, D. P. (2008) Double-edged swords as cancer therapeutics: simultaneously targeting p53 and NF-kappaB pathways. Nat Rev Drug Discov 7: 1031-1040

Di Croce, L.; Raker, V. A.; Corsaro, M.; Fazi, F.; Fanelli, M.; Faretta, M.; Fuks, F.; Lo Coco, F.; Kouzarides, T.; Nervi, C.; Minucci, S. & Pelicci, P. G. (2002) Methyltransferase recruitment and DNA hypermethylation of target promoters by an oncogenic transcription factor. Science 295: 1079-1082

Dijsselbloem, N.; Goriely, S.; Albarani, V.; Gerlo, S.; Francoz, S.; Marine, J. C.; Goldman, M.; Haegeman, G. & Vanden Berghe, W. (2007) A critical role for p53 in the control of NF-kappaB-dependent gene expression in TLR4-stimulated dendritic cells exposed to Genistein. J Immunol 178: 5048-5057

Dijsselbloem, N.; Vanden Berghe, W.; De Naeyer, A. & Haegeman, G. (2004) Soy isoflavone phyto-pharmaceuticals in interleukin-6 affections: multi-purpose nutraceuticals at the crossroad of hormone replacement, anti-cancer and anti-inflammatory therapy. Biochem Pharmacol 68: 1171-1185

Dolinoy, D. C.; Huang, D. & Jirtle, R. L. (2007) Maternal nutrient supplementation counteracts bisphenol A-induced DNA hypomethylation in early development. Proceedings of the National Academy of Sciences of the United States of America 104: 13056-13061

Dolinoy, D. C. & Jirtle, R. L. (2008) Environmental epigenomics in human health and disease. Environ Mol Mutagen 49: 4-8

Dolinoy, D. C.; Weidman, J. R.; Waterland, R. A. & Jirtle, R. L. (2006) Maternal genistein alters coat color and protects Avy mouse offspring from obesity by modifying the fetal epigenome. Environ Health Perspect 114: 567-572

Dong, J.; Jimi, E.; Zhong, H.; Hayden, M. S. & Ghosh, S. (2008) Repression of gene expression by unphosphorylated NF-kappaB p65 through epigenetic mechanisms. Genes and Development 22: 1159-1173

Eden, A.; Gaudet, F.; Waghmare, A. & Jaenisch, R. (2003) Chromosomal instability and tumors promoted by DNA hypomethylation. Science 300: 455

Edmunds, J. W. & Mahadevan, L. C. (2006) Cell signaling. Protein kinases seek close encounters with active genes. Science 313: 449-451

Eferl, R. & Wagner, E. F. (2003) AP-1: a double-edged sword in tumorigenesis. Nat Rev Cancer 3: 859-868

El-Osta, A.; Brasacchio, D.; Yao, D.; Pocai, A.; Jones, P. L.; Roeder, R. G.; Cooper, M. E. & Brownlee, M. (2008) Transient high glucose causes persistent epigenetic changes and altered gene expression during subsequent normoglycemia. J Exp Med 205: 2409-2417

El Gazzar, M.; Yoza, B. K.; Chen, X.; Garcia, B. A.; Young, N. L. & McCall, C. E. (2009) Chromatin-specific remodeling by HMGB1 and linker histone H1 silences proinflammatory genes during endotoxin tolerance. Mol Cell Biol 29: 1959-1971

El Gazzar, M.; Yoza, B. K.; Hu, J. Y.; Cousart, S. L. & McCall, C. E. (2007) Epigenetic silencing of tumor necrosis factor alpha during endotoxin tolerance. The Journal of biological chemistry 282: 26857-26864

Elsasser, S. J.; Allis, C. D. & Lewis, P. W. (2011) Cancer. New epigenetic drivers of cancers. Science 331: 1145-1146

Ernst, J. & Kellis, M. (2010) Discovery and characterization of chromatin states for systematic annotation of the human genome. Nature Biotechnology 28: 817-825

Ernst, J.; Kheradpour, P.; Mikkelsen, T. S.; Shoresh, N.; Ward, L. D.; Epstein, C. B.; Zhang, X.; Wang, L.; Issner, R.; Coyne, M.; Ku, M.; Durham, T.; Kellis, M. & Bernstein, B. E. (2011) Mapping and analysis of chromatin state dynamics in nine human cell types. Nature 473: 43-49

Esteller, M. (2007) Cancer epigenomics: DNA methylomes and histone-modification maps. Nat Rev Genet 8: 286-298

Esteller, M. (2008) Epigenetics in cancer. N Engl J Med 358: 1148-1159

Fang, M.; Chen, D. & Yang, C. S. (2007) Dietary polyphenols may affect DNA methylation. The Journal of nutrition 137: 223S-228S

Faulk, C. & Dolinoy, D. C. (2011) Timing is everything: The when and how of environmentally induced changes in the epigenome of animals. Epigenetics 6: 791-797

Ficz, G.; Branco, M. R.; Seisenberger, S.; Santos, F.; Krueger, F.; Hore, T. A.; Marques, C. J.; Andrews, S. & Reik, W. (2011) Dynamic regulation of 5-hydroxymethylcytosine in mouse ES cells and during differentiation. Nature 473: 398-402

Figueroa, M. E.; Abdel-Wahab, O.; Lu, C.; Ward, P. S.; Patel, J.; Shih, A.; Li, Y.; Bhagwat, N.; Vasanthakumar, A.; Fernandez, H. F.; Tallman, M. S.; Sun, Z.; Wolniak, K.; Peeters, J. K.; Liu, W.; Choe, S. E.; Fantin, V. R.; Paietta, E.; Lowenberg, B.; Licht, J. D. et al (2010) Leukemic IDH1 and IDH2 mutations result in a hypermethylation phenotype, disrupt TET2 function, and impair hematopoietic differentiation. Cancer Cell 18: 553-567

Fischle, W. (2008) Talk is cheap--cross-talk in establishment, maintenance, and readout of chromatin modifications. Genes and Development 22: 3375-3382

Fiskus, W.; Wang, Y.; Sreekumar, A.; Buckley, K. M.; Shi, H.; Jillella, A.; Ustun, C.; Rao, R.; Fernandez, P.; Chen, J.; Balusu, R.; Koul, S.; Atadja, P.; Marquez, V. E. & Bhalla, K. N. (2009) Combined epigenetic therapy with the histone methyltransferase EZH2 inhibitor 3-deazaneplanocin A and the histone deacetylase inhibitor panobinostat against human AML cells. Blood 114: 2733-2743

Folmer, F.; Orlikova, B.; Schnekenburger, M.; Dicato, M. & Diederich, M. (2010) Naturally occurring regulators of histone acetylation/deacetylation. Current Nutrition & Food Science 6: 78-99

Ford, E. & Thanos, D. (2010) The transcriptional code of human IFN-beta gene expression. Biochim Biophys Acta

Forneris, F.; Binda, C.; Battaglioli, E. & Mattevi, A. (2008) LSD1: oxidative chemistry for multifaceted functions in chromatin regulation. Trends in Biochemical Sciences 33: 181-189

Fraga, M. F.; Ballestar, E.; Paz, M. F.; Ropero, S.; Setien, F.; Ballestar, M. L.; Heine-Suner, D.; Cigudosa, J. C.; Urioste, M.; Benitez, J.; Boix-Chornet, M.; Sanchez-Aguilera, A.; Ling, C.; Carlsson, E.; Poulsen, P.; Vaag, A.; Stephan, Z.; Spector, T. D.; Wu, Y. Z.; Plass, C. et al (2005) Epigenetic differences arise during the lifetime of monozygotic twins. Proceedings of the National Academy of Sciences of the United States of America 102: 10604-10609

Franco, R.; Schoneveld, O.; Georgakilas, A. G. & Panayiotidis, M. I. (2008) Oxidative stress, DNA methylation and carcinogenesis. Cancer Lett 266: 6-11

Fujioka, M.; Wu, X. & Jaynes, J. B. (2009) A chromatin insulator mediates transgene homing and very long-range enhancer-promoter communication. Development 136: 3077-3087

Gallou-Kabani, C.; Vige, A.; Gross, M. S. & Junien, C. (2007) Nutri-epigenomics: lifelong remodelling of our epigenomes by nutritional and metabolic factors and beyond. Clin Chem Lab Med 45: 321-327

Garcia-Rivera, D.; Delgado, R.; Bougarne, N.; Haegeman, G. & Berghe, W. V. (2011) Gallic acid indanone and mangiferin xanthone are strong determinants of immunosuppressive anti-tumour effects of Mangifera indica L. bark in MDA-MB231 breast cancer cells. Cancer Lett 305: 21-31

Gasche, J. A.; Hoffmann, J.; Boland, C. R. & Goel, A. (2011) Interleukin-6 promotes tumorigenesis by altering DNA methylation in oral cancer cells. International Journal of Cancer 129: 1053-1063

Gaudet, F.; Hodgson, J. G.; Eden, A.; Jackson-Grusby, L.; Dausman, J.; Gray, J. W.; Leonhardt, H. & Jaenisch, R. (2003) Induction of tumors in mice by genomic hypomethylation. Science 300: 489-492

Gehani, S. S.; Agrawal-Singh, S.; Dietrich, N.; Christophersen, N. S.; Helin, K. & Hansen, K. (2010) Polycomb group protein displacement and gene activation through MSK-dependent H3K27me3S28 phosphorylation. Molecular Cell 39: 886-900

Gerlo, S.; Haegeman, G. & Vanden Berghe, W. (2008) Transcriptional regulation of autocrine IL-6 expression in multiple myeloma cells. Cell Signal 20: 1489-1496

Ghosh, S. & Hayden, M. S. (2008) New regulators of NF-kappaB in inflammation. Nat Rev Immunol 8: 837-848

Ghoshal, K.; Li, X.; Datta, J.; Bai, S.; Pogribny, I.; Pogribny, M.; Huang, Y.; Young, D. & Jacob, S. T. (2006) A folate- and methyl-deficient diet alters the expression of DNA methyltransferases and methyl CpG binding proteins involved in epigenetic gene silencing in livers of F344 rats. The Journal of nutrition 136: 1522-1527

Gluckman, P. D.; Hanson, M. A.; Cooper, C. & Thornburg, K. L. (2008) Effect of in utero and early-life conditions on adult health and disease. N Engl J Med 359: 61-73

Godfrey, K. M.; Gluckman, P. D. & Hanson, M. A. (2010) Developmental origins of metabolic disease: life course and intergenerational perspectives. Trends Endocrinol Metab 21: 199-205

Grivennikov, S.; Karin, E.; Terzic, J.; Mucida, D.; Yu, G. Y.; Vallabhapurapu, S.; Scheller, J.; Rose-John, S.; Cheroutre, H.; Eckmann, L. & Karin, M. (2009) IL-6 and Stat3 are required for survival of intestinal epithelial cells and development of colitis-associated cancer. Cancer Cell 15: 103-113

Grivennikov, S. I.; Greten, F. R. & Karin, M. (2010) Immunity, inflammation, and cancer. Cell 140: 883-899

Grivennikov, S. I. & Karin, M. (2010a) Dangerous liaisons: STAT3 and NF-κB collaboration and crosstalk in cancer. Cytokine & Growth Factor Reviews 21: 11-19

Grivennikov, S. I. & Karin, M. (2010b) Inflammation and oncogenesis: a vicious connection. Curr Opin Genet Dev 20: 65-71

Guil, S. & Esteller, M. (2009) DNA methylomes, histone codes and miRNAs: tying it all together. Int J Biochem Cell Biol 41: 87-95

Gupta, R. A.; Shah, N.; Wang, K. C.; Kim, J.; Horlings, H. M.; Wong, D. J.; Tsai, M. C.; Hung, T.; Argani, P.; Rinn, J. L.; Wang, Y.; Brzoska, P.; Kong, B.; Li, R.; West, R. B.; van de Vijver, M. J.; Sukumar, S. & Chang, H. Y. (2010) Long non-coding RNA HOTAIR reprograms chromatin state to promote cancer metastasis. Nature 464: 1071-1076

Hajkova, P.; Ancelin, K.; Waldmann, T.; Lacoste, N.; Lange, U. C.; Cesari, F.; Lee, C.; Almouzni, G.; Schneider, R. & Surani, M. A. (2008) Chromatin dynamics during epigenetic reprogramming in the mouse germ line. Nature 452: 877-881

Hakim, O.; Sung, M. H.; Voss, T. C.; Splinter, E.; John, S.; Sabo, P. J.; Thurman, R. E.; Stamatoyannopoulos, J. A.; de Laat, W. & Hager, G. L. (2011) Diverse gene reprogramming events occur in the same spatial clusters of distal regulatory elements. Genome Res 21: 697-706

Hamm, C. A. & Costa, F. F. (2011) The impact of epigenomics on future drug design and new therapies. Drug Discovery Today 16: 626-635

Hamm, C. A.; Xie, H.; Costa, F. F.; Vanin, E. F.; Seftor, E. A.; Sredni, S. T.; Bischof, J.; Wang, D.; Bonaldo, M. F.; Hendrix, M. J. & Soares, M. B. (2009) Global demethylation of rat chondrosarcoma cells after treatment with 5-aza-2'-deoxycytidine results in increased tumorigenicity. PLoS ONE 4: e8340

Hanahan, D. & Weinberg, Robert A. (2011) Hallmarks of Cancer: The Next Generation. Cell 144: 646-674

Harvey, A. (2008) Natural products in drug discovery. Drug Discovery Today 13: 894-901

Hauser, A. T. & Jung, M. (2008) Targeting epigenetic mechanisms: potential of natural products in cancer chemoprevention. Planta Medica 74: 1593-1601

Hayden, M. S. & Ghosh, S. (2008) Shared principles in NF-kappaB signaling. Cell 132: 344-362

Herceg, Z. (2007) Epigenetics and cancer: towards an evaluation of the impact of environmental and dietary factors. Mutagenesis 22: 91-103

Hervouet, E.; Vallette, F. M. & Cartron, P. F. (2009) Dnmt3/transcription factor interactions as crucial players in targeted DNA methylation. Epigenetics 4: 487-499

Hesson, L. B.; Hitchins, M. P. & Ward, R. L. (2010) Epimutations and cancer predisposition: importance and mechanisms. Curr Opin Genet Dev 20: 290-298

Hochberg, Z.; Feil, R.; Constancia, M.; Fraga, M.; Junien, C.; Carel, J. C.; Boileau, P.; Le Bouc, Y.; Deal, C. L.; Lillycrop, K.; Scharfmann, R.; Sheppard, A.; Skinner, M.; Szyf, M.; Waterland, R. A.; Waxman, D. J.; Whitelaw, E.; Ong, K. & Albertsson-Wikland, K. (2011) Child health, developmental plasticity, and epigenetic programming. Endocr Rev 32: 159-224

Hodge, D. R.; Cho, E.; Copeland, T. D.; Guszczynski, T.; Yang, E.; Seth, A. K. & Farrar, W. L. (2007) IL-6 enhances the nuclear translocation of DNA cytosine-5-methyltransferase 1 (DNMT1) via phosphorylation of the nuclear localization sequence by the AKT kinase. Cancer Genomics Proteomics 4: 387-398

Hodge, D. R.; Peng, B.; Cherry, J. C.; Hurt, E. M.; Fox, S. D.; Kelley, J. A.; Munroe, D. J. & Farrar, W. L. (2005a) Interleukin 6 supports the maintenance of p53 tumor suppressor gene promoter methylation. Cancer Res 65: 4673-4682

Hodge, D. R.; Peng, B.; Pompeia, C.; Thomas, S.; Cho, E.; Clausen, P. A.; Marquez, V. E. & Farrar, W. L. (2005b) Epigenetic Silencing of Manganese Superoxide Dismutase (SOD-2) in KAS 6/1 Human Multiple Myeloma Cells Increases Cell Proliferation. Cancer Biol Ther 4

Hodge, D. R.; Xiao, W.; Clausen, P. A.; Heidecker, G.; Szyf, M. & Farrar, W. L. (2001) Interleukin-6 regulation of the human DNA methyltransferase (HDNMT) gene in human erythroleukemia cells. The Journal of biological chemistry 276: 39508-39511

Hotamisligil, G. S. (2010) Endoplasmic reticulum stress and the inflammatory basis of metabolic disease. Cell 140: 900-917

Hurt, E. M. & Farrar, W. L. (2008) Cancer stem cells: the seeds of metastasis? Mol Interv 8: 140-142

Iliopoulos, D.; Hirsch, H. A. & Struhl, K. (2009) An epigenetic switch involving NF-kappaB, Lin28, Let-7 MicroRNA, and IL6 links inflammation to cell transformation. Cell 139: 693-706

Iliopoulos, D.; Hirsch, H. A.; Wang, G. & Struhl, K. (2011) Inducible formation of breast cancer stem cells and their dynamic equilibrium with non-stem cancer cells via IL6 secretion. Proceedings of the National Academy of Sciences of the United States of America 108: 1397-1402

Iliopoulos, D.; Jaeger, S. A.; Hirsch, H. A.; Bulyk, M. L. & Struhl, K. (2010) STAT3 Activation of miR-21 and miR-181b-1 via PTEN and CYLD Are Part of the Epigenetic Switch Linking Inflammation to Cancer. Molecular Cell 39: 493-506

Illi, B.; Colussi, C.; Grasselli, A.; Farsetti, A.; Capogrossi, M. C. & Gaetano, C. (2009) NO sparks off chromatin: tales of a multifaceted epigenetic regulator. Pharmacol Ther 123: 344-352

Imai, S. & Guarente, L. (2010) Ten years of NAD-dependent SIR2 family deacetylases: implications for metabolic diseases. Trends Pharmacol Sci 31: 212-220

Iqbal, K.; Jin, S. G.; Pfeifer, G. P. & Szabo, P. E. (2011) Reprogramming of the paternal genome upon fertilization involves genome-wide oxidation of 5-methylcytosine. Proceedings of the National Academy of Sciences of the United States of America 108: 3642-3647

Jackson, A. A.; Burdge, G. C. & Lillycrop, K. A. (2010) Diet, nutrition and modulation of genomic expression in fetal origins of adult disease. World Review of Nutrition and Dietetics 101: 56-72

Jenuwein, T. & Allis, C. D. (2001) Translating the histone code. Science 293: 1074-1080.

Jirtle, R. L. & Skinner, M. K. (2007) Environmental epigenomics and disease susceptibility. Nat Rev Genet 8: 253-262

Jones, P. A. & Liang, G. (2009) Rethinking how DNA methylation patterns are maintained. Nat Rev Genet 10: 805-811

Jones, R. S. (2007) Epigenetics: reversing the 'irreversible'. Nature 450: 357-359

Kaileh, M.; Vanden Berghe, W.; Heyerick, A.; Horion, J.; Piette, J.; Libert, C.; De Keukeleire, D.; Essawi, T. & Haegeman, G. (2007) Withaferin a strongly elicits IkappaB kinase beta hyperphosphorylation concomitant with potent inhibition of its kinase activity. The Journal of biological chemistry 282: 4253-4264

Kaminsky, Z. A.; Tang, T.; Wang, S. C.; Ptak, C.; Oh, G. H.; Wong, A. H.; Feldcamp, L. A.; Virtanen, C.; Halfvarson, J.; Tysk, C.; McRae, A. F.; Visscher, P. M.; Montgomery, G. W.; Gottesman, II; Martin, N. G. & Petronis, A. (2009) DNA methylation profiles in monozygotic and dizygotic twins. Nature Genetics 41: 240-245

Kangaspeska, S.; Stride, B.; Metivier, R.; Polycarpou-Schwarz, M.; Ibberson, D.; Carmouche, R. P.; Benes, V.; Gannon, F. & Reid, G. (2008) Transient cyclical methylation of promoter DNA. Nature 452: 112-115

Karin, M. (2006) Nuclear factor-kappaB in cancer development and progression. Nature 441: 431-436

Karin, M. & Greten, F. R. (2005) NF-kappaB: linking inflammation and immunity to cancer development and progression. Nat Rev Immunol 5: 749-759

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

Kawasaki, B. T.; Hurt, E. M.; Mistree, T. & Farrar, W. L. (2008a) Targeting cancer stem cells with phytochemicals. Mol Interv 8: 174-184

Khanna, D.; Sethi, G.; Ahn, K. S.; Pandey, M. K.; Kunnumakkara, A. B.; Sung, B.; Aggarwal, A. & Aggarwal, B. B. (2007) Natural products as a gold mine for arthritis treatment. Curr Opin Pharmacol 7: 344-351

Kim, J. M.; Hong, K.; Lee, J. H.; Lee, S. & Chang, N. (2009a) Effect of folate deficiency on placental DNA methylation in hyperhomocysteinemic rats. J Nutr Biochem 20: 172-176

Kim, K. C.; Friso, S. & Choi, S. W. (2009b) DNA methylation, an epigenetic mechanism connecting folate to healthy embryonic development and aging. J Nutr Biochem 20: 917-926

Kirk, H.; Cefalu, W. T.; Ribnicky, D.; Liu, Z. & Eilertsen, K. J. (2008) Botanicals as epigenetic modulators for mechanisms contributing to development of metabolic syndrome. Metabolism: Clinical and Experimental 57: S16-23

Ko, M.; Huang, Y.; Jankowska, A. M.; Pape, U. J.; Tahiliani, M.; Bandukwala, H. S.; An, J.; Lamperti, E. D.; Koh, K. P.; Ganetzky, R.; Liu, X. S.; Aravind, L.; Agarwal, S.; Maciejewski, J. P. & Rao, A. (2010) Impaired hydroxylation of 5-methylcytosine in myeloid cancers with mutant TET2. Nature 468: 839-843

Kok, T. M.; Breda, S. G. & Manson, M. M. (2008) Mechanisms of combined action of different chemopreventive dietary compounds. European Journal of Nutrition 47: 51-59

Kominsky, D. J.; Keely, S.; MacManus, C. F.; Glover, L. E.; Scully, M.; Collins, C. B.; Bowers, B. E.; Campbell, E. L. & Colgan, S. P. (2011) An Endogenously Anti-Inflammatory Role for Methylation in Mucosal Inflammation Identified through Metabolite Profiling. The Journal of Immunology 186: 6505-6514

Kontogiorgis, C.; Bompou, E.; Ntella, M. & Vanden Berghe, W. (2010) Natural Products from Mediterranean Diet: From Anti-Inflammatory Agents to Dietary Epigenetic Modulators. Anti-Inflammatory & Anti-Allergy Agents in Medicinal Chemistry 6: 101-124

Kujjo, L. L.; Chang, E. A.; Pereira, R. J.; Dhar, S.; Marrero-Rosado, B.; Sengupta, S.; Wang, H.; Cibelli, J. B. & Perez, G. I. (2011) Chemotherapy-induced late transgenerational effects in mice. PLoS ONE 6: e17877

Kuniyasu, H. (2008) The Roles of Dietary PPARgamma Ligands for Metastasis in Colorectal Cancer. PPAR research 2008: 529720

Ladurner, A. G. (2009) Chromatin places metabolism center stage. Cell 138: 18-20

Lai, A. Y. & Wade, P. A. (2011) Cancer biology and NuRD: a multifaceted chromatin remodelling complex. Nat Rev Cancer

Lande-Diner, L. & Cedar, H. (2005) Silence of the genes--mechanisms of long-term repression. Nature Reviews Genetics 6: 648-654

Law, J. A. & Jacobsen, S. E. (2010) Establishing, maintaining and modifying DNA methylation patterns in plants and animals. Nat Rev Genet 11: 204-220

Lee, B. M. & Mahadevan, L. C. (2009) Stability of histone modifications across mammalian genomes: implications for 'epigenetic' marking. J Cell Biochem 108: 22-34

Lee, D. H.; Jacobs, D. R., Jr. & Porta, M. (2009) Hypothesis: a unifying mechanism for nutrition and chemicals as lifelong modulators of DNA hypomethylation. Environ Health Perspect 117: 1799-1802

Lee, K. W.; Bode, A. M. & Dong, Z. (2011) Molecular targets of phytochemicals for cancer prevention. Nature Reviews Cancer 11: 211-218

Lees-Murdock, D. J. & Walsh, C. P. (2008) DNA methylation reprogramming in the germ line. Advances in Experimental Medicine and Biology 626: 1-15

Li, J. W. H. & Vederas, J. C. (2009) Drug Discovery and Natural Products: End of an Era or an Endless Frontier? Science 325: 161-165

Li, N.; Grivennikov, Sergei I. & Karin, M. (2011) The Unholy Trinity: Inflammation, Cytokines, and STAT3 Shape The Cancer Microenvironment. Cancer Cell 19: 429-431

Li, Y.; Kong, D.; Wang, Z. & Sarkar, F. H. (2010) Regulation of microRNAs by Natural Agents: An Emerging Field in Chemoprevention and Chemotherapy Research. Pharmaceutical Research 27: 1027-1041

Lieberman-Aiden, E.; van Berkum, N. L.; Williams, L.; Imakaev, M.; Ragoczy, T.; Telling, A.; Amit, I.; Lajoie, B. R.; Sabo, P. J.; Dorschner, M. O.; Sandstrom, R.; Bernstein, B.; Bender, M. A.; Groudine, M.; Gnirke, A.; Stamatoyannopoulos, J.; Mirny, L. A.; Lander, E. S. & Dekker, J. (2009) Comprehensive mapping of long-range interactions reveals folding principles of the human genome. Science 326: 289-293

Link, A.; Balaguer, F. & Goel, A. (2010) Cancer chemoprevention by dietary polyphenols: Promising role for epigenetics. Biochem Pharmacol

Liu, M.; Sakamaki, T.; Casimiro, M. C.; Willmarth, N. E.; Quong, A. A.; Ju, X.; Ojeifo, J.; Jiao, X.; Yeow, W. S.; Katiyar, S.; Shirley, L. A.; Joyce, D.; Lisanti, M. P.; Albanese, C. & Pestell, R. G. (2010a) The canonical NF-kappaB pathway governs mammary tumorigenesis in transgenic mice and tumor stem cell expansion. Cancer Res 70: 10464-10473

Liu, S.; Liu, Z.; Xie, Z.; Pang, J.; Yu, J.; Lehmann, E.; Huynh, L.; Vukosavljevic, T.; Takeki, M.; Klisovic, R. B.; Baiocchi, R. A.; Blum, W.; Porcu, P.; Garzon, R.; Byrd, J. C.; Perrotti, D.; Caligiuri, M. A.; Chan, K. K.; Wu, L. C. & Marcucci, G. (2008) Bortezomib induces DNA hypomethylation and silenced gene transcription by interfering with Sp1/NF-kappaB-dependent DNA methyltransferase activity in acute myeloid leukemia. Blood 111: 2364-2373

Liu, X.; Wang, X.; Zhang, J.; Lam, E. K.; Shin, V. Y.; Cheng, A. S.; Yu, J.; Chan, F. K.; Sung, J. J. & Jin, H. C. (2010b) Warburg effect revisited: an epigenetic link between glycolysis and gastric carcinogenesis. Oncogene 29: 442-450

Liu, Y.; Mayo, M. W.; Nagji, A. S.; Smith, P. W.; Ramsey, C. S.; Li, D. & Jones, D. R. (2011) Phosphorylation of RelA/p65 promotes DNMT-1 recruitment to chromatin and represses transcription of the tumor metastasis suppressor gene BRMS1. Oncogene

Lujambio, A.; Calin, G. A.; Villanueva, A.; Ropero, S.; Sanchez-Cespedes, M.; Blanco, D.; Montuenga, L. M.; Rossi, S.; Nicoloso, M. S.; Faller, W. J.; Gallagher, W. M.; Eccles, S. A.; Croce, C. M. & Esteller, M. (2008) A microRNA DNA methylation signature for human cancer metastasis. Proceedings of the National Academy of Sciences of the United States of America 105: 13556-13561

Lujambio, A. & Esteller, M. (2007) CpG island hypermethylation of tumor suppressor microRNAs in human cancer. Cell Cycle 6: 1455-1459

Lujambio, A. & Esteller, M. (2009) How epigenetics can explain human metastasis: a new role for microRNAs. Cell Cycle 8: 377-382

Lumey, L. H. & Stein, A. D. (2009) Transgenerational effects of prenatal exposure to the Dutch famine. BJOG 116: 868; author reply 868

Luo, J. & Kuo, M. H. (2009) Linking nutrient metabolism to epigenetics. Cell Science Reviews 6: 49-54

Maeda, G.; Chiba, T.; Kawashiri, S.; Satoh, T. & Imai, K. (2007) Epigenetic inactivation of IkappaB Kinase-alpha in oral carcinomas and tumor progression. Clinical Cancer Research 13: 5041-5047

Maeda, S.; Hikiba, Y.; Sakamoto, K.; Nakagawa, H.; Hirata, Y.; Hayakawa, Y.; Yanai, A.; Ogura, K.; Karin, M. & Omata, M. (2009) Ikappa B kinasebeta/nuclear factor-kappaB activation controls the development of liver metastasis by way of interleukin-6 expression. Hepatology 50: 1851-1860

Maher, B. (2008) Personal genomes: The case of the missing heritability. Nature 456: 18-21

Mahfouz, M. M. (2010) RNA-directed DNA methylation: Mechanisms and functions. Plant Signal Behav 5: 806-816

Mai, A.; Cheng, D.; Bedford, M. T.; Valente, S.; Nebbioso, A.; Perrone, A.; Brosch, G.; Sbardella, G.; De Bellis, F.; Miceli, M. & Altucci, L. (2008) Epigenetic multiple ligands: mixed histone/protein methyltransferase, acetyltransferase, and class III deacetylase (sirtuin) inhibitors. J Med Chem 51: 2279-2290

Manach, C. & Donovan, J. L. (2004) Pharmacokinetics and metabolism of dietary flavonoids in humans. Free Radic Res 38: 771-785

Manach, C.; Mazur, A. & Scalbert, A. (2005a) Polyphenols and prevention of cardiovascular diseases. Curr Opin Lipidol 16: 77-84

Manach, C.; Scalbert, A.; Morand, C.; Remesy, C. & Jimenez, L. (2004) Polyphenols: food sources and bioavailability. Am J Clin Nutr 79: 727-747

Manach, C.; Williamson, G.; Morand, C.; Scalbert, A. & Remesy, C. (2005b) Bioavailability and bioefficacy of polyphenols in humans. I. Review of 97 bioavailability studies. Am J Clin Nutr 81: 230S-242S

Mandl, J.; Meszaros, T.; Banhegyi, G.; Hunyady, L. & Csala, M. (2009) Endoplasmic reticulum: nutrient sensor in physiology and pathology. Trends Endocrinol Metab 20: 194-201

Manolio, T. A.; Collins, F. S.; Cox, N. J.; Goldstein, D. B.; Hindorff, L. A.; Hunter, D. J.; McCarthy, M. I.; Ramos, E. M.; Cardon, L. R.; Chakravarti, A.; Cho, J. H.; Guttmacher, A. E.; Kong, A.; Kruglyak, L.; Mardis, E.; Rotimi, C. N.; Slatkin, M.; Valle, D.; Whittemore, A. S.; Boehnke, M. et al (2009) Finding the missing heritability of complex diseases. Nature 461: 747-753

Mantovani, A.; Allavena, P.; Sica, A. & Balkwill, F. (2008) Cancer-related inflammation. Nature 454: 436-444

Margueron, R.; Trojer, P. & Reinberg, D. (2005) The key to development: interpreting the histone code? Curr Opin Genet Dev 15: 163-176

Martinez-Outschoorn, U. E.; Prisco, M.; Ertel, A.; Tsirigos, A.; Lin, Z.; Pavlides, S.; Wang, C.; Flomenberg, N.; Knudsen, E. S.; Howell, A.; Pestell, R. G.; Sotgia, F. & Lisanti, M. P. (2011) Ketones and lactate increase cancer cell "stemness," driving recurrence, metastasis and poor clinical outcome in breast cancer: Achieving personalized medicine via Metabolo-Genomics. Cell Cycle 10: 1271-1286

Mathews, L. A.; Crea, F. & Farrar, W. L. (2009) Epigenetic gene regulation in stem cells and correlation to cancer. Differentiation 78: 1-17

Mattick, J. S.; Amaral, P. P.; Dinger, M. E.; Mercer, T. R. & Mehler, M. F. (2009a) RNA regulation of epigenetic processes. BioEssays 31: 51-59

Mattick, J. S.; Taft, R. J. & Faulkner, G. J. (2009b) A global view of genomic information - moving beyond the gene and the master regulator. Trends Genet

Medzhitov, R. & Horng, T. (2009) Transcriptional control of the inflammatory response. Nat Rev Immunol 9: 692-703

Meeran, S. M.; Ahmed, A. & Tollefsbol, T. O. (2010) Epigenetic targets of bioactive dietary components for cancer prevention and therapy. Clinical Epigenetics 1: 101-116

Meng, F.; Wehbe-Janek, H.; Henson, R.; Smith, H. & Patel, T. (2008) Epigenetic regulation of microRNA-370 by interleukin-6 in malignant human cholangiocytes. Oncogene 27: 378-386

Messi, M.; Giacchetto, I.; Nagata, K.; Lanzavecchia, A.; Natoli, G. & Sallusto, F. (2003) Memory and flexibility of cytokine gene expression as separable properties of human T(H)1 and T(H)2 lymphocytes. Nat Immunol 4: 78-86

Messina, M. & Hilakivi-Clarke, L. (2009) Early intake appears to be the key to the proposed protective effects of soy intake against breast cancer. Nutr Cancer 61: 792-798

Metivier, R.; Gallais, R.; Tiffoche, C.; Le Peron, C.; Jurkowska, R. Z.; Carmouche, R. P.; Ibberson, D.; Barath, P.; Demay, F.; Reid, G.; Benes, V.; Jeltsch, A.; Gannon, F. & Salbert, G. (2008) Cyclical DNA methylation of a transcriptionally active promoter. Nature 452: 45-50

Metivier, R.; Reid, G. & Gannon, F. (2006) Transcription in four dimensions: nuclear receptor-directed initiation of gene expression. EMBO Rep 7: 161-167

Min, J.; Zaslavsky, A.; Fedele, G.; McLaughlin, S. K.; Reczek, E. E.; De Raedt, T.; Guney, I.; Strochlic, D. E.; Macconaill, L. E.; Beroukhim, R.; Bronson, R. T.; Ryeom, S.; Hahn, W. C.; Loda, M. & Cichowski, K. (2010) An oncogene-tumor suppressor cascade drives metastatic prostate cancer by coordinately activating Ras and nuclear factor-kappaB. Nature Medicine 16: 286-294

Miranda, T. B. & Jones, P. A. (2007) DNA methylation: the nuts and bolts of repression. Journal of Cellular Physiology 213: 384-390

Mulero-Navarro, S. & Esteller, M. (2008) Chromatin remodeling factor CHD5 is silenced by promoter CpG island hypermethylation in human cancer. Epigenetics 3: 210-215

Myers, R. M.; Stamatoyannopoulos, J.; Snyder, M.; Dunham, I.; Hardison, R. C.; Bernstein, B. E.; Gingeras, T. R.; Kent, W. J.; Birney, E.; Wold, B. & Crawford, G. E. (2011) A user's guide to the encyclopedia of DNA elements (ENCODE). PLoS Biol 9: e1001046

Nakanishi, C. & Toi, M. (2005) Nuclear factor-kappaB inhibitors as sensitizers to anticancer drugs. Nat Rev Cancer 5: 297-309

Natoli, G. (2010) Maintaining Cell Identity through Global Control of Genomic Organization. Immunity 33: 12-24

Natoli, G. & De Santa, F. (2006) Shaping alternative NF-kappaB-dependent gene expression programs: new clues to specificity. Cell Death Differ 13: 693-696

Natoli, G.; Ghisletti, S. & Barozzi, I. (2011) The genomic landscapes of inflammation. Genes & Development 25: 101-106

Natoli, G.; Saccani, S.; Bosisio, D. & Marazzi, I. (2005) Interactions of NF-kappaB with chromatin: the art of being at the right place at the right time. Nat Immunol 6: 439-445

Naugler, W. E. & Karin, M. (2008) The wolf in sheep's clothing: the role of interleukin-6 in immunity, inflammation and cancer. Trends in Molecular Medicine 14: 109-119

Ndlovu, M. N.; Denis, H. & Fuks, F. (2011) Exposing the DNA methylome iceberg. Trends in Biochemical Sciences

Ndlovu, N.; Van Lint, C.; Van Wesemael, K.; Callebert, P.; Chalbos, D.; Haegeman, G. & Vanden Berghe, W. (2009) Hyperactivated NF-{kappa}B and AP-1 transcription factors promote highly accessible chromatin and constitutive transcription across the interleukin-6 gene promoter in metastatic breast cancer cells. Mol Cell Biol 29: 5488-5504

Newbold, R. R.; Padilla-Banks, E. & Jefferson, W. N. (2009) Environmental estrogens and obesity. Mol Cell Endocrinol 304: 84-89

Nolis, I. K.; McKay, D. J.; Mantouvalou, E.; Lomvardas, S.; Merika, M. & Thanos, D. (2009) Transcription factors mediate long-range enhancer-promoter interactions. Proceedings of the National Academy of Sciences of the United States of America 106: 20222-20227

Nunez, E.; Fu, X. D. & Rosenfeld, M. G. (2009) Nuclear organization in the 3D space of the nucleus - cause or consequence? Curr Opin Genet Dev 19: 424-436

O'Dea, E. & Hoffmann, A. (2010) The regulatory logic of the NF-kappaB signaling system. Cold Spring Harb Perspect Biol 2: a000216

O'Gorman, A.; Colleran, A.; Ryan, A.; Mann, J. & Egan, L. J. (2010) Regulation of NF-{kappa}B responses by epigenetic suppression of I{kappa}B{alpha} expression in HCT116 intestinal epithelial cells. American Journal of Physiology Gastrointestinal and Liver Physiology

Olefsky, J. M. (2009) IKKepsilon: a bridge between obesity and inflammation. Cell 138: 834-836

Pacholec, M.; Bleasdale, J. E.; Chrunyk, B.; Cunningham, D.; Flynn, D.; Garofalo, R. S.; Griffith, D.; Griffor, M.; Loulakis, P.; Pabst, B.; Qiu, X.; Stockman, B.; Thanabal, V.; Varghese, A.; Ward, J.; Withka, J. & Ahn, K. (2010) SRT1720, SRT2183, SRT1460, and resveratrol are not direct activators of SIRT1. The Journal of biological chemistry 285: 8340-8351

Painter, R. C.; Osmond, C.; Gluckman, P.; Hanson, M.; Phillips, D. I. & Roseboom, T. J. (2008) Transgenerational effects of prenatal exposure to the Dutch famine on neonatal adiposity and health in later life. BJOG 115: 1243-1249

Parasramka, M. A.; Ho, E.; Williams, D. E. & Dashwood, R. H. (2011) MicroRNAs, diet, and cancer: New mechanistic insights on the epigenetic actions of phytochemicals. Molecular Carcinogenesis: n/a-n/a

Park, E. J.; Lee, J. H.; Yu, G.-Y.; He, G.; Ali, S. R.; Holzer, R. G.; Österreicher, C. H.; Takahashi, H. & Karin, M. (2010) Dietary and Genetic Obesity Promote Liver Inflammation and Tumorigenesis by Enhancing IL-6 and TNF Expression. Cell 140: 197-208

Pasparakis, M. (2009) Regulation of tissue homeostasis by NF-kappaB signalling: implications for inflammatory diseases. Nat Rev Immunol 9: 778-788

Paul, A. T.; Gohil, V. M. & Bhutani, K. K. (2006) Modulating TNF-alpha signaling with natural products. Drug Discov Today 11: 725-732

Peng, B.; Hodge, D. R.; Thomas, S. B.; Cherry, J. M.; Munroe, D. J.; Pompeia, C.; Xiao, W. & Farrar, W. L. (2005) Epigenetic silencing of the human nucleotide excision repair gene, hHR23B, in interleukin-6-responsive multiple myeloma KAS-6/1 cells. The Journal of biological chemistry 280: 4182-4187

Perillo, B.; Ombra, M. N.; Bertoni, A.; Cuozzo, C.; Sacchetti, S.; Sasso, A.; Chiariotti, L.; Malorni, A.; Abbondanza, C. & Avvedimento, E. V. (2008) DNA Oxidation as Triggered by H3K9me2 Demethylation Drives Estrogen-Induced Gene Expression. Science 319: 202-206

Perissi, V.; Jepsen, K.; Glass, C. K. & Rosenfeld, M. G. (2010) Deconstructing repression: evolving models of co-repressor action. Nat Rev Genet 11: 109-123

Perissi, V. & Rosenfeld, M. G. (2005) Controlling nuclear receptors: the circular logic of cofactor cycles. Nat Rev Mol Cell Biol 6: 542-554

Perkins, N. D. (2007) Integrating cell-signalling pathways with NF-kappaB and IKK function. Nat Rev Mol Cell Biol 8: 49-62

Petronis, A. (2006) Epigenetics and twins: three variations on the theme. Trends in Genetics 22: 347-350

Pogribny, I. P.; Tryndyak, V. P.; Muskhelishvili, L.; Rusyn, I. & Ross, S. A. (2007) Methyl deficiency, alterations in global histone modifications, and carcinogenesis. The Journal of nutrition 137: 216S-222S

Pompeia, C.; Hodge, D. R.; Plass, C.; Wu, Y. Z.; Marquez, V. E.; Kelley, J. A. & Farrar, W. L. (2004) Microarray analysis of epigenetic silencing of gene expression in the KAS-6/1 multiple myeloma cell line. Cancer Res 64: 3465-3473

Puto, L. A. & Reed, J. C. (2008) Daxx represses RelB target promoters via DNA methyltransferase recruitment and DNA hypermethylation. Genes Dev 22: 998-1010

Rajasekhar, V. K.; Studer, L.; Gerald, W.; Socci, N. D. & Scher, H. I. (2011) Tumour-initiating stem-like cells in human prostate cancer exhibit increased NF-kappaB signalling. Nat Commun 2: 162

Rakyan, V. K.; Down, T. A.; Balding, D. J. & Beck, S. (2011) Epigenome-wide association studies for common human diseases. Nat Rev Genet 12: 529-541

Ramirez-Carrozzi, V. R.; Braas, D.; Bhatt, D. M.; Cheng, C. S.; Hong, C.; Doty, K. R.; Black, J. C.; Hoffmann, A.; Carey, M. & Smale, S. T. (2009) A unifying model for the selective

regulation of inducible transcription by CpG islands and nucleosome remodeling. Cell 138: 114-128

Ramirez-Carrozzi, V. R.; Nazarian, A. A.; Li, C. C.; Gore, S. L.; Sridharan, R.; Imbalzano, A. N. & Smale, S. T. (2006) Selective and antagonistic functions of SWI/SNF and Mi-2beta nucleosome remodeling complexes during an inflammatory response. Genes Dev 20: 282-296

Raney, B. J.; Cline, M. S.; Rosenbloom, K. R.; Dreszer, T. R.; Learned, K.; Barber, G. P.; Meyer, L. R.; Sloan, C. A.; Malladi, V. S.; Roskin, K. M.; Suh, B. B.; Hinrichs, A. S.; Clawson, H.; Zweig, A. S.; Kirkup, V.; Fujita, P. A.; Rhead, B.; Smith, K. E.; Pohl, A.; Kuhn, R. M. et al (2011) ENCODE whole-genome data in the UCSC genome browser (2011 update). Nucleic Acids Res 39: D871-875

Rathmell, J. C. & Newgard, C. B. (2009) Biochemistry. A glucose-to-gene link. Science 324: 1021-1022

Reuter, S.; Gupta, S. C.; Chaturvedi, M. M. & Aggarwal, B. B. (2010) Oxidative stress, inflammation, and cancer: how are they linked? Free Radic Biol Med 49: 1603-1616

Rios, J. L.; Recio, M. C.; Escandell, J. M. & Andujar, I. (2009) Inhibition of transcription factors by plant-derived compounds and their implications in inflammation and cancer. Curr Pharm Des 15: 1212-1237

Robertson, A. G.; Bilenky, M.; Tam, A.; Zhao, Y.; Zeng, T.; Thiessen, N.; Cezard, T.; Fejes, A. P.; Wederell, E. D.; Cullum, R.; Euskirchen, G.; Krzywinski, M.; Birol, I.; Snyder, M.; Hoodless, P. A.; Hirst, M.; Marra, M. A. & Jones, S. J. (2008) Genome-wide relationship between histone H3 lysine 4 mono- and tri-methylation and transcription factor binding. Genome Research 18: 1906-1917

Robertson, K. D. (2005) DNA methylation and human disease. Nature Reviews Genetics 6: 597-610

Rohwer, N.; Dame, C.; Haugstetter, A.; Wiedenmann, B.; Detjen, K.; Schmitt, C. A. & Cramer, T. (2010) Hypoxia-inducible factor 1alpha determines gastric cancer chemosensitivity via modulation of p53 and NF-kappaB. PLoS ONE 5: e12038

Roseboom, T.; de Rooij, S. & Painter, R. (2006) The Dutch famine and its long-term consequences for adult health. Early Human Development 82: 485-491

Rosenfeld, M. G.; Lunyak, V. V. & Glass, C. K. (2006) Sensors and signals: a coactivator/corepressor/epigenetic code for integrating signal-dependent programs of transcriptional response. Genes Dev 20: 1405-1428

Ruden, D. M.; De Luca, M.; Garfinkel, M. D.; Bynum, K. L. & Lu, X. (2005a) Drosophila nutrigenomics can provide clues to human gene-nutrient interactions. Annu Rev Nutr 25: 499-522

Ruden, D. M.; Xiao, L.; Garfinkel, M. D. & Lu, X. (2005b) Hsp90 and environmental impacts on epigenetic states: a model for the trans-generational effects of diethylstibesterol on uterine development and cancer. Hum Mol Genet 14 Spec No 1: R149-155

Santourlidis, S.; Warskulat, U.; Florl, A. R.; Maas, S.; Pulte, T.; Fischer, J.; Muller, W. & Schulz, W. A. (2001) Hypermethylation of the tumor necrosis factor receptor superfamily 6 (APT1, Fas, CD95/Apo-1) gene promoter at rel/nuclear factor kappaB sites in prostatic carcinoma. Mol Carcinog 32: 36-43

Scarano, M. I.; Strazzullo, M.; Matarazzo, M. R. & D'Esposito, M. (2005) DNA methylation 40 years later: Its role in human health and disease. Journal of Cellular Physiology 204: 21-35

Schreiber, S. L. & Bernstein, B. E. (2002) Signaling network model of chromatin. Cell 111: 771-778

Seet, B. T.; Dikic, I.; Zhou, M. M. & Pawson, T. (2006) Reading protein modifications with interaction domains. Nat Rev Mol Cell Biol 7: 473-483

Sharma, P.; Senthilkumar, R. D.; Brahmachari, V.; Sundaramoorthy, E.; Mahajan, A.; Sharma, A. & Sengupta, S. (2006) Mining literature for a comprehensive pathway analysis: a case study for retrieval of homocysteine related genes for genetic and epigenetic studies. Lipids Health Dis 5: 1

Sharma, S. V.; Lee, D. Y.; Li, B.; Quinlan, M. P.; Takahashi, F.; Maheswaran, S.; McDermott, U.; Azizian, N.; Zou, L.; Fischbach, M. A.; Wong, K. K.; Brandstetter, K.; Wittner, B.; Ramaswamy, S.; Classon, M. & Settleman, J. (2010) A chromatin-mediated reversible drug-tolerant state in cancer cell subpopulations. Cell 141: 69-80

Shu, X. O.; Zheng, Y.; Cai, H.; Gu, K.; Chen, Z.; Zheng, W. & Lu, W. (2009) Soy food intake and breast cancer survival. Jama 302: 2437-2443

Shytle, R. D.; Ehrhart, J.; Tan, J.; Vila, J.; Cole, M.; Sanberg, C. D.; Sanberg, P. R. & Bickford, P. C. (2007) Oxidative stress of neural, hematopoietic, and stem cells: protection by natural compounds. Rejuvenation Res 10: 173-178

Singh, S. (2007) From Exotic Spice to Modern Drug? Cell 130: 765-768

Skinner, M. K.; Manikkam, M. & Guerrero-Bosagna, C. (2011) Epigenetic transgenerational actions of endocrine disruptors. Reproductive Toxicology 31: 337-343

Solinas, G. & Karin, M. (2010) JNK1 and IKK{beta}: molecular links between obesity and metabolic dysfunction. Faseb J: in press

Sollars, V.; Lu, X.; Xiao, L.; Wang, X.; Garfinkel, M. D. & Ruden, D. M. (2003) Evidence for an epigenetic mechanism by which Hsp90 acts as a capacitor for morphological evolution. Nature Genetics 33: 70-74

Sporn, M. B. (2011) Perspective: The big C - for Chemoprevention. Nature 471: S10-11

Sung, B.;Prasad, S.;Yadav, V. R.;Lavasanifar, A. & Aggarwal, B. B. (2011) Cancer and diet: How are they related? Free Radic Res 45: 864-879

Surani, M. A.; Ancelin, K.; Hajkova, P.; Lange, U. C.; Payer, B.; Western, P. & Saitou, M. (2004) Mechanism of mouse germ cell specification: a genetic program regulating epigenetic reprogramming. Cold Spring Harbor Symposia on Quantitative Biology 69: 1-9

Surh, Y. J. (2003) Cancer chemoprevention with dietary phytochemicals. Nat Rev Cancer 3: 768-780

Suttana, W.; Mankhetkorn, S.; Poompimon, W.; Palagani, A.; Zhokhov, S.; Gerlo, S.; Haegeman, G. & Berghe, W. (2010) Differential chemosensitization of P-glycoprotein overexpressing K562/Adr cells by withaferin A and Siamois polyphenols. Molecular Cancer 9: 99

Suzuki, T. & Miyata, N. (2006) Epigenetic control using natural products and synthetic molecules. Curr Med Chem 13: 935-958

Szarc vel Szic, K.; Ndlovu, M. N.; Haegeman, G. & Vanden Berghe, W. (2010) Nature or nurture: Let food be your epigenetic medicine in chronic inflammatory disorders. Biochemical Pharmacology 80: 1816-1832

Taft, R. J.; Glazov, E. A.; Cloonan, N.; Simons, C.; Stephen, S.; Faulkner, G. J.; Lassmann, T.; Forrest, A. R.; Grimmond, S. M.; Schroder, K.; Irvine, K.; Arakawa, T.; Nakamura, M.; Kubosaki, A.; Hayashida, K.; Kawazu, C.; Murata, M.; Nishiyori, H.; Fukuda,

S.; Kawai, J. et al (2009a) Tiny RNAs associated with transcription start sites in animals. Nat Genet 41: 572-578

Taft, R. J.; Pang, K. C.; Mercer, T. R.; Dinger, M. & Mattick, J. S. (2009b) Non-coding RNAs: regulators of disease. J Pathol 220: 126-139

Tennant, D. A.; Duran, R. V. & Gottlieb, E. (2010) Targeting metabolic transformation for cancer therapy. Nat Rev Cancer 10: 267-277

Teperino, R.; Schoonjans, K. & Auwerx, J. (2010) Histone methyl transferases and demethylases; can they link metabolism and transcription? Cell Metab 12: 321-327

Teschendorff, A. E.; Menon, U.; Gentry-Maharaj, A.; Ramus, S. J.; Weisenberger, D. J.; Shen, H.; Campan, M.; Noushmehr, H.; Bell, C. G.; Maxwell, A. P.; Savage, D. A.; Mueller-Holzner, E.; Marth, C.; Kocjan, G.; Gayther, S. A.; Jones, A.; Beck, S.; Wagner, W.; Laird, P. W.; Jacobs, I. J. et al (2010) Age-dependent DNA methylation of genes that are suppressed in stem cells is a hallmark of cancer. Genome Research 20: 440-446

Tolhuis, B.; Blom, M.; Kerkhoven, R. M.; Pagie, L.; Teunissen, H.; Nieuwland, M.; Simonis, M.; de Laat, W.; van Lohuizen, M. & van Steensel, B. (2011) Interactions among Polycomb domains are guided by chromosome architecture. PLoS Genet 7: e1001343

Tsai, M. C.; Manor, O.; Wan, Y.; Mosammaparast, N.; Wang, J. K.; Lan, F.; Shi, Y.; Segal, E. & Chang, H. Y. (2010) Long Noncoding RNA as Modular Scaffold of Histone Modification Complexes. Science

Ulrich, C. M.; Reed, M. C. & Nijhout, H. F. (2008) Modeling folate, one-carbon metabolism, and DNA methylation. Nutr Rev 66 Suppl 1: S27-30

Vaissiere, T.; Sawan, C. & Herceg, Z. (2008) Epigenetic interplay between histone modifications and DNA methylation in gene silencing. Mutation Research 659: 40-48

van Steensel, B. (2011) Chromatin: constructing the big picture. The EMBO Journal 30: 1885-1895

van Uden, P.; Kenneth, N. S.; Webster, R.; Muller, H. A.; Mudie, S. & Rocha, S. (2011) Evolutionary conserved regulation of HIF-1beta by NF-kappaB. PLoS Genet 7: e1001285

Vanden Berghe, W.; De Bosscher, K.; Boone, E.; Plaisance, S. & Haegeman, G. (1999a) The nuclear factor-kappaB engages CBP/p300 and histone acetyltransferase activity for transcriptional activation of the interleukin-6 gene promoter. The Journal of biological chemistry 274: 32091-32098

Vanden Berghe, W.; Dijsselbloem, N.; Vermeulen, L.; Ndlovu, N.; Boone, E. & Haegeman, G. (2006a) Attenuation of Mitogen- and Stress-Activated Protein Kinase-1-Driven Nuclear Factor-{kappa}B Gene Expression by Soy Isoflavones Does Not Require Estrogenic Activity. Cancer Res 66: 4852-4862

Vanden Berghe, W.; Francesconi, E.; De Bosscher, K.; Resche-Rigon, M. & Haegeman, G. (1999b) Dissociated glucocorticoids with anti-inflammatory potential repress interleukin-6 gene expression by a nuclear factor-kappaB-dependent mechanism. Mol Pharmacol 56: 797-806

Vanden Berghe, W.; Ndlovu, M. N.; Hoya-Arias, R.; Dijsselbloem, N.; Gerlo, S. & Haegeman, G. (2006b) Keeping up NF-kappaB appearances: epigenetic control of immunity or inflammation-triggered epigenetics. Biochem Pharmacol 72: 1114-1131

Vanden Berghe, W.; Plaisance, S.; Boone, E.; De Bosscher, K.; Schmitz, M. L.; Fiers, W. & Haegeman, G. (1998) p38 and extracellular signal-regulated kinase mitogen-

activated protein kinase pathways are required for nuclear factor-kappaB p65 transactivation mediated by tumor necrosis factor. The Journal of biological chemistry 273: 3285-3290

Vanden Berghe, W.; De Naeyer, A.; Dijsselbloem, N.; David, J. P.; De Keukeleire, D. & Haegeman, G. (2011) Attenuation of ERK/RSK2-Driven NFkappaB Gene Expression and Cancer Cell Proliferation by Kurarinone, a Lavandulyl Flavanone Isolated from Sophora flavescens Ait. Roots. Endocr Metab Immune Disord Drug Targets, in press

Vaquero, A. & Reinberg, D. (2009) Calorie restriction and the exercise of chromatin. Genes Dev 23: 1849-1869

Varela, I.; Tarpey, P.; Raine, K.; Huang, D.; Ong, C. K.; Stephens, P.; Davies, H.; Jones, D.; Lin, M. L.; Teague, J.; Bignell, G.; Butler, A.; Cho, J.; Dalgliesh, G. L.; Galappaththige, D.; Greenman, C.; Hardy, C.; Jia, M.; Latimer, C.; Lau, K. W. et al (2011) Exome sequencing identifies frequent mutation of the SWI/SNF complex gene PBRM1 in renal carcinoma. Nature 469: 539-542

Vermeulen, L.; Berghe, W. V.; Beck, I. M.; De Bosscher, K. & Haegeman, G. (2009) The versatile role of MSKs in transcriptional regulation. Trends Biochem Sci 34: 311-318

Vermeulen, L.; De Wilde, G.; Van Damme, P.; Vanden Berghe, W. & Haegeman, G. (2003) Transcriptional activation of the NF-kappaB p65 subunit by mitogen- and stress-activated protein kinase-1 (MSK1). EMBO J 22: 1313-1324

Viatour, P.; Merville, M. P.; Bours, V. & Chariot, A. (2005) Phosphorylation of NF-kappaB and IkappaB proteins: implications in cancer and inflammation. Trends Biochem Sci 30: 43-52

Vire, E.; Brenner, C.; Deplus, R.; Blanchon, L.; Fraga, M.; Didelot, C.; Morey, L.; Van Eynde, A.; Bernard, D.; Vanderwinden, J. M.; Bollen, M.; Esteller, M.; Di Croce, L.; de Launoit, Y. & Fuks, F. (2006) The Polycomb group protein EZH2 directly controls DNA methylation. Nature 439: 871-874

Wallace, D. C. (2010a) Bioenergetics and the epigenome: interface between the environment and genes in common diseases. Dev Disabil Res Rev 16: 114-119

Wallace, D.C. (2010b) The epigenome and the mitochondrion: bioenergetics and the environment [corrected]. Genes Dev 24: 1571-1573

Wang, H.; Lathia, J. D.; Wu, Q.; Wang, J.; Li, Z.; Heddleston, J. M.; Eyler, C. E.; Elderbroom, J.; Gallagher, J.; Schuschu, J.; MacSwords, J.; Cao, Y.; McLendon, R. E.; Wang, X. F.; Hjelmeland, A. B. & Rich, J. N. (2009) Targeting interleukin 6 signaling suppresses glioma stem cell survival and tumor growth. Stem cells (Dayton, Ohio) 27: 2393-2404

Wang, L.; Chia, N. C.; Lu, X. & Ruden, D. M. (2011) Hypothesis: Environmental regulation of 5-hydroxymethylcytosine by oxidative stress. Epigenetics 6: 853-856

Waterland, R. A. (2009) Is epigenetics an important link between early life events and adult disease? Horm Res 71 Suppl 1: 13-16

Waterland, R. A. & Jirtle, R. L. (2004) Early nutrition, epigenetic changes at transposons and imprinted genes, and enhanced susceptibility to adult chronic diseases. Nutrition 20: 63-68

Waterland, R. A.; Travisano, M.; Tahiliani, K. G.; Rached, M. T. & Mirza, S. (2008) Methyl donor supplementation prevents transgenerational amplification of obesity. Int J Obes (Lond) 32: 1373-1379

Weaver, I.C. (2009) Shaping adult phenotypes through early life environments. Birth Defects Research Part C, Embryo Today 87: 314-326

Weisz, L.; Damalas, A.; Liontos, M.; Karakaidos, P.; Fontemaggi, G.; Maor-Aloni, R.; Kalis, M.; Levrero, M.; Strano, S.; Gorgoulis, V. G.; Rotter, V.; Blandino, G. & Oren, M. (2007) Mutant p53 enhances nuclear factor kappaB activation by tumor necrosis factor alpha in cancer cells. Cancer Res 67: 2396-2401

Wellen, K. E.; Hatzivassiliou, G.; Sachdeva, U. M.; Bui, T. V.; Cross, J. R. & Thompson, C. B. (2009) ATP-citrate lyase links cellular metabolism to histone acetylation. Science 324: 1076-1080

Werner, S. L.; Barken, D. & Hoffmann, A. (2005) Stimulus specificity of gene expression programs determined by temporal control of IKK activity. Science 309: 1857-1861

Whittle, J. R.; Powell, M. J.; Popov, V. M.; Shirley, L. A.; Wang, C. & Pestell, R. G. (2007) Sirtuins, nuclear hormone receptor acetylation and transcriptional regulation. Trends Endocrinol Metab 18: 356-364

Widschwendter, M. & Jones, P. A. (2002) DNA methylation and breast carcinogenesis. Oncogene 21: 5462-5482

Wiench, M.; John, S.; Baek, S.; Johnson, T. A.; Sung, M. H.; Escobar, T.; Simmons, C. A.; Pearce, K. H.; Biddie, S. C.; Sabo, P. J.; Thurman, R. E.; Stamatoyannopoulos, J. A. & Hager, G. L. (2011) DNA methylation status predicts cell type-specific enhancer activity. EMBO J

Wigle, T. J.; Herold, J. M.; Senisterra, G. A.; Vedadi, M.; Kireev, D. B.; Arrowsmith, C. H.; Frye, S. V. & Janzen, W. P. Screening for inhibitors of low-affinity epigenetic peptide-protein interactions: an AlphaScreen-based assay for antagonists of methyl-lysine binding proteins. J Biomol Screen 15: 62-71

Williamson, G. & Manach, C. (2005) Bioavailability and bioefficacy of polyphenols in humans. II. Review of 93 intervention studies. Am J Clin Nutr 81: 243S-255S

Wossidlo, M.; Arand, J.; Sebastiano, V.; Lepikhov, K.; Boiani, M.; Reinhardt, R.; Scholer, H. & Walter, J. (2010) Dynamic link of DNA demethylation, DNA strand breaks and repair in mouse zygotes. EMBO J 29: 1877-1888

Wossidlo, M.; Nakamura, T.; Lepikhov, K.; Marques, C. J.; Zakhartchenko, V.; Boiani, M.; Arand, J.; Nakano, T.; Reik, W. & Walter, J. (2011) 5-Hydroxymethylcytosine in the mammalian zygote is linked with epigenetic reprogramming. Nat Commun 2: 241

Yang, H. & Dou, Q. P. (2010) Targeting apoptosis pathway with natural terpenoids: implications for treatment of breast and prostate cancer. Curr Drug Targets 11: 733-744

Youngson, N. A. & Whitelaw, E. (2008) Transgenerational epigenetic effects. Annual Review of Genomics and Human Genetics 9: 233-257

Yu, H.; Pardoll, D. & Jove, R. (2009) STATs in cancer inflammation and immunity: a leading role for STAT3. Nature Reviews Cancer 9: 798-809

Zhang, X.; Zhang, G.; Zhang, H.; Karin, M.; Bai, H. & Cai, D. (2008) Hypothalamic IKKbeta/NF-kappaB and ER stress link overnutrition to energy imbalance and obesity. Cell 135: 61-73

Zheng, Y. G.; Wu, J.; Chen, Z. & Goodman, M. (2008) Chemical regulation of epigenetic modifications: opportunities for new cancer therapy. Med Res Rev 28: 645-687

Zhou, J.; Zhang, H.; Gu, P.; Bai, J.; Margolick, J. B. & Zhang, Y. (2008) NF-kappaB pathway inhibitors preferentially inhibit breast cancer stem-like cells. Breast Cancer Res Treat 111: 419-427