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Mini-review

The epigenome and cancer prevention: A complex story of dietary supplementation

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ABSTRACT

Epigenetic changes have been implicated in virtually all types of human malignancies. In contrast to genetic changes, epigenetic changes occur in a gradual manner during the tumorigenic process and they are potentially reversible. Because epigenetic changes have frequently been detected in high-risk populations, they are attractive targets to prevent the initiation of premalignant lesions or their advance to a malignant stage. A wide range of chemical entities has been found capable of altering the epigenome in animal models and humans. Epidemiological and laboratory-based studies suggested that these agents may have an anti-neoplastic effect against different cancer types. Several of these agents have been tested as dietary supplements, often with conflicting results. In this review, we discuss recent developments in our understanding of agents capable of modulating the epigenome and their potential to prevent human cancer when administered as dietary supplements.

1. Introduction

Epigenetics can be defined heritable changes in gene expression that occur without DNA sequence changes. It triggers initiation and/or maintaining of cell-type-specific transcriptional profiles and key role in cancer development. Three distinct mechanisms are well known to regulate the epigenome: DNA methylation, histone modifications, and small-interfering RNAs. Epigenetic processes by these mechanisms include genomic imprinting, gene silencing, X chromosome inactivation, reprogramming in transferred nuclei, and carcinogenesis [1–4]. Epigenetic mechanisms are also believed to mediate gene-environment interactions and may serve as an interface between the genome and its environment [5]. Various environmental/lifestyle stressors and endogenous cues may induce alteration in the epigenome, thus deregulating different cellular process that may result in various disease including cancer.

Importantly, epigenetic changes in comparison with genetic ones are reversible and are acquired in a gradual manner. These distinguishing features make epigenetic changes attractive not only for cancer therapy but also for cancer prevention. Recent studies provide evidence that dietary factors including food supplementation may have an important impact on epigenetic states [6–8], underscoring the need for identifying epigenetic targets and critical window of vulnerability to environmental/dietary modulation, both of which may prove highly useful in the design of novels strategies for cancer control. The work on epigenetic mechanisms in regulation of cellular processes and epigenetic modifications in cancer cells induced by environmental factors have been recently reviewed [9,10]. In this review, we will focus on recent evidence demonstrating the impact of dietary supplementation on epigenome and its potential cancer prevention.

2. Epigenetic mechanisms

2.1. DNA methylation

DNA methylation is an epigenetic mechanism that allows the regulation of transcription via the addition of methyl groups from S-adenosyl-L-methionine to the 5-carbon (C^5) of the nucleotide cytosine. In general, DNA methylation in gene promoter regions results in gene silencing likely because of steric inhibition of transcription complexes binding to regulatory DNA. This reaction is catalyzed by DNA methyltransferases (Dnmt): Dnmt1, Dnmt2, Dnmt3a, Dnmt3b, and DnmtL. For example, Dnmt1 is thought to be the main enzyme that maintains DNA methyltransferases because it shows a preference for hemi-methylated DNA substrates. Dnmt3A and 3B are responsible for methylation of new CpG sites. In addition, DNA methylation can result in the recruitment of proteins that bind methylated CpG sequences (methyl-CpG-binding domain proteins) complexed with histone deacetylases (HDACs) and HMTs prompting coordinated epigenetic modifications of the surrounding chromatin. Although less frequent, methylation in

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the asymmetric non-CpG sequences CpC, CpA and CpT has been repeatedly reported, first in plant and more recently in mammalian genomes. Non-CpG DNA methylation was strictly allele-specific, never affecting the wild type locus in heterozygotes and reported to be maintained by Dnmt1 [11].

Compared to DNA methylation, DNA demethylation remains unclear. A recent study indicates that the human TET proteins could catalyze the conversion of 5-methylcytosine (5mC) of DNA to 5-hydroxymethylcytosine (5hmC), 5-formylcytosine (5Fc) and 5-carboxylcytosine (5caC), that are involved in DNA demethylation [12–14]. Additionally, TET2, a member of the TET family, was found to be frequently mutated in myeloid malignancies with low level of 5hmC [15]. The roles of global and gene-specific DNA demethylation are related to early development, reprogramming during gametogenesis and cloning, memory formation and neurogenesis, immune response and tumorigenesis [16,17]. Here, we will focus on the role of DNA methylation with exposure to specific diet and on approaches aiming to explore cancer prevention.

2.2. Histone modification

A nucleosome, which consists of 146 bp DNA and an octamer of histone proteins (H2A, H2B, H3 and H4), which can regulate transcriptional processes through postsynthetic modifications of DNA and histones. Histone can be modified by methylation, acetylation, phosphorylation, biotinylation, ubiquitination, sumoylation, and ADP-ribosylation. Although a number of histone modifications undoubtedly play important roles in epigenetic regulation, acetylation and methylation are the two main histone modifications that have been clinically associated with pathological epigenetic disruptions in cancer cells. In particular, the loss of acetylation and methylation of specific residues in core histones H3 and H4 have been identified as a marker of tumor cells [18,19].

Histone acetylation consists in the transfer of an acetyl group from acetyl-CoA to the lysine ε-amino groups on the N-terminal tails of histones. Histone acetyltransferase (HAT) and histone deacetylase (HDAC) regulate the steady-state balance of histone acetylation. Interestingly, HDAC inhibitors have been recognized as potential cancer therapeutic agents, because they induce cell cycle arrest and apoptosis by enhancing the expression of certain proapoptotic or cell cycle mediating genes [20]. Because inhibition of HDAC could derepress epigenetically silenced genes in cancer cells, it has been investigated whether certain bioactive food components can act as HDAC inhibitors; e.g. sulforafane, an isothiocyanate from broccoli and broccoli sprouts, resveratrol, curcumin, an organosulfur compound from garlic, and butyrate [21–24].

2.3. Non-coding RNAs (long and microRNAs)

The human genome contains only 20,000 protein-coding genes, representing <2% of the total genome, whereas a substantial fraction of the human genome can be transcribed, yielding many short or noncoding RNAs (ncRNAs) with limited protein-coding capacity [25]. Among them, the most extensively studied ncRNAs are microRNA (miRNA, 20–22 nt), which are evolutionarily conserved and are located within the introns and exons of protein-coding genes (70%) or in intergenic regions (30%). Numerous miRNA expression profiling and functional studies have associated with cancer progression, diagnosis, prognosis, and treatment. About 50% of annotated human miRNAs are mapped in fragile regions of chromosomes, which are areas of the genome that are associated with various human cancers [26]. Genomic instability that disrupts miRNA-target gene regulation has been associated with an increasing number of cancer types [27]. Inhibition of global miRNA processing have also led to increased tumorigenicity and transformation [28] .

During the last few years, evidence of complex, long ncRNA (typically >200 nt) mediated epigenetic control systems has increased dramatically. Multiple lines of evidence increasingly link mutations and dysregulations of lncRNAs to diverse human diseases. Alterations in the primary structure, secondary structure, and expression levels of lncRNAs as well as their cognate RNA-binding proteins underlie diseases ranging from neurodegeneration to cancer [29–31]. Growing evidence indicates that dietary factors, such as genistein and curcumin, play an important role in carcinogenesis through modulation of miRNA expression [32–34]. Recently, Zhang et al., reported that miRNAs (namely miR168a) from plants may regulate LDL levels in mammalian plasma, consistent with the silencing effect on LDLRAP1 mRNA and protein [35].

2.4. Reprogramming of epigenetic patterns during embryonic development and cell differentiation

Epigenetic patterns of the genome become reprogrammed, during germline development and early embryonic development after fertilization. There are two waves of global genome demethylation on embryonic development and DNA methylation resetting during lineage differenatiation. The parental genome undergoes active DNA demethylation after fertilization, and replication-dependent passive demethylation occurs in the preimplantation embryo. At the same time, some gene silencing events, such as the inactivation of the paternal X chromosome, are actually being established, accompanied by histone modifications. Thereafter, lineage-specific *de novo* methylation occurs following implantation, concurrent with the lineage allocation. In addition, it creates a cellular memory, which is maintained throughout life and in some instances across generations [36,37]. Recently, DNA methylation has been found in cord blood haematopoietic stem cells from intrauterine growth restriction neonates, indicating that epigenetic modifications are a means for remembering fetal adaptations in humans [38]. Dysregulation of developmental programming is believed to induce abnormal DNA methylation of specific genes that permit them to undergo inappropriate expression in adult life, leading to disease development. Therefore, variation in environmental exposures during critical periods could result in epigenetic changes and phenotypic differences later in life.

Epigenetic effects of maternal supplementation on offspring during early development have been demonstated using several animal models. For example, using the agouti viable yellow (A^{vy}: which is variable coat-color phenotype) and axin 1 fused ($Axin1^{Fu}$: which causes a variably expressed tail kink mice), methylation changes at the loci whose methylation pattern governs development abnormalities and epigenetic changes as well as dramatic phenotypic outcomes have been characterized [39,40]. For example, a maternal diet rich in methyl donors in A^{vy} mice causes DNA methylation of a metastable epiallele, preventing offspring from becoming fat, diabetic, and cancer-prone [41]. The studies correlating maternal diet and epigenetic changes in the offspring carried out using animal models may ultimately lead to the development of genomic approaches for their identification in humans, although the question of whether these findings can be extrapolated to humans have been raised [41].

2.5. Dietary modulation in epigenome: the role of one-carbon metabolism

Methylation reactions, catalyzed by methyltransferases, depend on the pool of the methyl donor S-adenosylmethionine (SAM) in the body. Methyl-tetrahydrofolate (THF) acts as a methyl group donor for the production of THF and is a precursor for homocysteine conversion to methionine. Methionine is then further activated to