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Review

Epigenetic regulation of active Chinese herbal components for cancer prevention and treatment: A follow-up review

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ABSTRACT

Epigenetic modifications include DNA methylation, histone modification, and other patterns. These processes are associated with carcinogenesis and cancer progression. Thus, epigenetic modification-related enzymes, such as DNA methyltransferases (DNMTs), histone methyltransferases (HMTs), histone demethylases (HDMTs), histone acetyltransferases (HATs), and histone deacetylases (HDACs), as well as some related proteins, including methyl-CpG binding proteins (MBPs) and DNMT1-associated protein (DMAP 1), are considered as potential targets for cancer prevention and therapy. Numerous natural compounds, mainly derived from Chinese herbs and chemically ranging from polyphenols and flavonoids to mineral salts, inhibit the growth and development of various cancers by targeting multiple genetic and epigenetic alterations. This review summarizes the epigenetic mechanisms by which active compounds from Chinese herbs exert their anti-cancer effect. A subset of these compounds, such as curcumin and resveratrol, affect multiple epigenetic processes, including DNMT inhibition, HDAC inactivation, MBP suppression, HAT activation, and microRNA modulation. Other compounds also regulate epigenetic modification processes, but the underlying mechanisms and clear targets remain unknown. Accordingly, further studies are required.

Contents

Abbreviations: DNMT, DNA methyltransferase; HMT, histone methytransferase; HDMT, histone demethylase; HAT, histone acetylatransferase; HDAC, histone deacetylase; MBP, methy-CpG binding protein; DMAP1, DNMT1-associated protein; MBD, methy-CpG binding domain; FDA, Food and Drug Administration; CGIs, CpG islands; KMT, histone lysine methyltransferase; KDMT, histone lysine demethylase; SUV, suppressor of variegation; EZH, enhancer of zeste proteins; Trx, trithorax; LSD1, lysine specific demethylase 1; JmjC, jumonji domain-containing; EGCG, (−)-epigallocatechin-3-gallate; CARM1, coavtivator-associated arginine methyltransferase.

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1. Introduction

Epigenetics is a study addressing the reversible and environment-driven modifications of gene expression and function rather than altering DNA sequence itself [1]. These dynamic modifications, frequently occurring during mitosis and meiosis, consist of many patterns including DNA methylation, histone modification, chromatin remodeling, genomic imprinting, X chromosome inactivation, and RNA interference [2,3]. By targeting various functional genes in cellular biology, epigenetics has transformed our perspective on genomes, and raises a number of novel insights in disease treatments.

DNA methylation, histone modification, and small noncoding microRNAs (miRNAs), the most commonly dysregulated epigenetic changes, have been extensively investigated in various diseases, especially in cancers [4]. The enzymes associated with these epigenetic modification patterns, such as DNA methyltransferases (DNMTs), histone methyltransferases (HMTs), histone demethylases (HDMTs), histone acetyltransferases (HATs), histone deacetylases (HDACs), as well as ribonucleases *Drosha* and *Dicer*, are essential for epigenetic regulations. At the meantime, some functional proteins including methyl-CpG binding proteins (MBPs) and DNMT1-associated protein (DMAP1) are also critical for certain gene epigenetical modifications. The gene expressions regulated by these epigenetic enzymes play important roles in multiple biological processes such as cell proliferation, differentiation, metabolism, and programmed death. Overwhelming evidences demonstrated that the dysfunction and inactivation of epigenetic-associated enzymes and proteins resulted in numerous diseases, such as liver [5] and cardiovascular diseases [6,7], especially in various cancers including lung [8] and colon cancers [9], as well as leukemia [10] and melanoma [11]. For instance, a number of genes involved in cell cycle and apoptosis (e.g., *CDKN2A* [5,8–10,12], *CDKN2B* [10], *DAPK1* [10], and *TP53* [10]), DNA repair (e.g., *GSTP1* [5,8]), signal transduction (e.g., *RASSF1A* [5], *APC* [13–16]), and tumor invasion or metastasis (e.g., *CDH1* [9]) can be epigenetically silenced by DNMTs through the promoter hypermethylation in various diseases including cancers. Furthermore, histone lysine residues are critical targets for epigenetical modification. *TIMP3*, a gene negatively regulating tumor cell invasion, is transcriptionally activated in lung cancer through KDM1A-catalyzed histone demethylation [17]. Moreover, the expressions of certain genes can be altered by different epigenetical mechanisms. *TP53* is inactivated through H3K9 deacetylation in pancreatic cancer [18], whereas *TP53* silencing is attributed to its promoter hypermethylation in leukemia [10]. By targeting numerous gene transcriptional or post-transcriptional alterations, epigenetic modifications serve as novel targets for cancer prevention and treatment.

Although over 170 anticancer drugs have been approved by the US Food and Drug Administration (FDA), only 6 agents target epigenetical processes including 2 DNMT inhibitors (azacitidine and decitabine) and 4 HDAC inhibitors (vorinostat, romidepsin, belinostat, and panobinostat) [19]. However, the unfavorable side effects occurred along with the anti-tumor effectiveness of these epigenetic agents, such as myelosuppression [20], acquired drug resistance [21], and secondary pneumonia [22,23]. Apart from these, they also exhibited low efficacy against solid tumors [24,25]. Thus, these epigenetic anti-cancer agents are limited to hematological malignancy treatments.

With high efficacy and low toxicity, natural active compounds from diet and Chinese herbs exhibit extensive bioactivities, which subsequently mediate multiple physical and pathological processes. For instance, emerging evidences suggested that curcumin [26], resveratrol [27], and green tea polyphenols [28–30], which are proven low toxic plant-derived compounds, could exert high efficacy in cancer treatment, even cancer prevention through optimizing immune responses and tumor microenvironments [31–33], reversing tumor multidrug resistance [34–36], as well as targeting multiple molecules and signaling pathways associated with cancer initiation and development. Furthermore, some of these active compounds have been proven to modify epigenetic patterns of multiple oncogenes and tumor suppressor genes.

In decades, approximately half of the FDA-approved newly discovered anti-cancer agents are of or derived from natural origins [37]. Given the great proportions of epigenetic alterations mediated by natural compounds, clearly describing the underlying mechanisms will benefit the search for novel anti-cancer agents in cancer prevention and treatment. This review aims to systematically summarize the epigenetic mechanisms by which Chinese herbal active compounds exert their anti-cancer effects. Our study provides a basis for future investigations and clinical uses of Chinese herbs, as well as proposes novel medical applications for epigenetical modulators.

2. Aberrant epigenetic alterations in cancer

2.1. DNA methylation

DNA methylation, the first described covalent modification of DNA, is perhaps the most extensively characterized chromatin modification [38]. Today, DNA methylation is a known common event occurring during cell growth, differentiation, and development in nearly every tissue [39]. The methylation of the 5-carbon on cytosine residues (5mC) in CpG dinucleotides (CGIs) mainly occurs within centromeres, telomeres, inactive X-chromosomes, and repeat sequences [40,41].

Members with catalytic activities of DNMT family including DNMT1, DNMT3A, and DNMT3B are responsible for DNA methylation. DNMT1 is a maintenance methyltransferase that recognizes hemimethylated DNA and that methylates CpG dinucleotides in newly-synthesized DNAs during DNA replication [42]. DNMT3A and DNMT3B function primarily as *de novo* methyltransferases to methylate previously unmethylated DNA during embryogenesis [43]. Typically, CpG dinucleotides in gene promoter regions are unmethylated or hypomethylated [41], whereas, majority of CpG dinucleotides in intergenic repeat sequences, such as ribosomal DNA repeats, satellite repeats, or centromeric repeats, are often hypermethylated, contributing to chromatin stability [44]. Unfortunately, DNMT3A mutations were observed in about 25% of patients that suffer from acute myeloid leukemia [45]. Further studies revealed that DNMT3A mutations mediated the epigenetic reactivation of the leukemogenic factor MEIS1 in acute myeloid leukemia [46]. These findings indicate that DNMTs mutations contribute to human malignancies (Fig. 1).