FEBS Letters 585 (2011) 2129–2136

journal homepage: www.FEBSLetters.org

Review

An overview of epigenetics and chemoprevention

Yi-Wen Huang [a,1], Chieh-Ti Kuo [b], Kristen Stoner [b], Tim H.-Y. Huang [a], Li-Shu Wang [b,*]

[a] Human Cancer Genetics Program, Comprehensive Cancer Center, The Ohio State University, Columbus, OH 43210, United States
[b] Comprehensive Cancer Center, College of Medicine, The Ohio State University, Columbus, OH 43210, United States

ARTICLE INFO

Article history:
Received 15 September 2010
Revised 30 October 2010
Accepted 2 November 2010
Available online 5 November 2010

Edited by Jean-Pierre Issa and Wilhelm Just

Keywords:
DNA methylation
Epigenome
Cancer prevention

ABSTRACT

It is now appreciated that both genetic alteration, e.g. mutations, and aberrant epigenetic changes, e.g. DNA methylation, cause cancer. Epigenetic dysregulation is potentially reversible which makes it attractive as targets for cancer prevention. Synthetic drugs targeting enzymes, e.g. DNA methyltransferase and histone deacetylase, that regulate epigenetic patterns are active in clinical settings. In addition, dietary factors have been suggested to have potential to reverse aberrant epigenetic patterns. Uncovering the human epigenome can lead us to better understand the dynamics of DNA methylation in disease progression which can further assist in cancer prevention.

Published by Elsevier B.V. on behalf of the Federation of European Biochemical Societies.

1. Introduction

Epigenetics is defined as the study of heritable modifications on chromatin, without changing the nucleotide sequence of DNA, that regulates gene expression [1]. Gene silencing caused by epigenetic alternations has been associated with all stages of tumor development including initiation, progression, invasion, and metastasis. In comparison to genetic DNA coding which provides the blueprint for the manufacture of proteins to be made for a living cell, epigenetic information provides instructions on how, where, and when the genetic information should be used [1]. Although it is clear that genetic alternations, e.g. mutations, either germ line or somatic, cause cancer, aberrant epigenetic alternations are now appreciated as crucial processes in cancer development [2,3]. However, unlike genetic alternations which are almost impossible to reverse, the potential reversibility of epigenetic patterns suggests that it is a viable target for the prevention and/or treatment of cancers [2–4]. This review presents recent findings on the mechanisms causing epigenetic dysregulation and the clinical implications of epigenetic changes in cancer prevention and risk assessment.

2. Epigenetic alternations in carcinogenesis

2.1. Epigenetic patterns in normal and cancerous cells

Epigenetic mediated gene silencing can be generally divided into three related processes: DNA methylation, chromatin remodeling, and histone modification [5]. The best characterized and studied epigenetic modification is DNA methylation especially in the promoter regions of genes that regulate important cellular functions. A critical step in DNA methylation involves DNA methyltransferases (DNMTs). These enzymes transfer methyl group from *S*-adenosylmethionine (SAM) to the 5 position of the cytosine ring. As shown in Fig. 1, in general, CpG islands in promoter regions of genes in normal cells are protected against methylation. Only small portion of genes with promoter CpG islands are methylated in cancer cells. Importantly, these genes are involved in regulation of crucial cellular functions and encoding for cell cycle regulation (e.g. $p16^{INK4a}$, p15, $p14^{ARF}$), DNA repair (e.g. MLH1, GST3), tumor

Abbreviations: DNMT, DNA methyltransferase; SAM, *S*-adenosylmethionine; HAT, histone acetylase; HDAC, histone deacetylase; MBD, methyl-CpG-binding domain; IBD, inflammatory bowel disease; SFRP, secreted frizzled-related protein; APC, adenomatous polyposis coli; ACF, aberrant crypt foci; DES, diethylstilbestrol; S1P, sphingosine-1-phosphate; SphK2, sphingosine kinase 2; SAHA, suberoylanilide hydroxamic acid; TSA, trichostatin; BRBs, freeze-dried black raspberries; WIF, Wnt inhibitory factor; EGCG, (−)-epigallocatechin 3-gallate; RAR, retinoic acid receptor; NSCLC, non-small-cell lung cancer; CDH13, cadherin 13; RASSF1A, ras association domain family protein 1A; PITX2, pituitary homeobox 2; COMT, catechol-*o*-methyltransferase; CYP, cytochrome P450; NAT1, *N*-acetyltransferase type 1; SULT1A1, sulfotransferase 1A1; CIMP, CpG island methylator phenotype; BMP-4, bone morphogenetic protein-4; FGF4, fibroblast growth factor 4; CDO1, cysteine dioxygenase 1; MGMT, *O*-6-methylguanine-DNA methyltransferase; 5-FU, 5-fluorouracil

* Corresponding author. Address: Comprehensive Cancer Center, The Ohio State University, 2001 Polaris PKWY, Columbus, OH 43210, United States.

E-mail addresses: yi-wen.huang@osumc.edu (Y.-W. Huang), li-shu.wang@osumc.edu (L.-S. Wang).

[1] Co-corresponding author. Address: Human Cancer Genetics Program, Comprehensive Cancer Center, The Ohio State University, 460 W 12th Ave Columbus, Columbus, OH 43210, United States.

0014-5793/$36.00 Published by Elsevier B.V. on behalf of the Federation of European Biochemical Societies.
doi:10.1016/j.febslet.2010.11.002

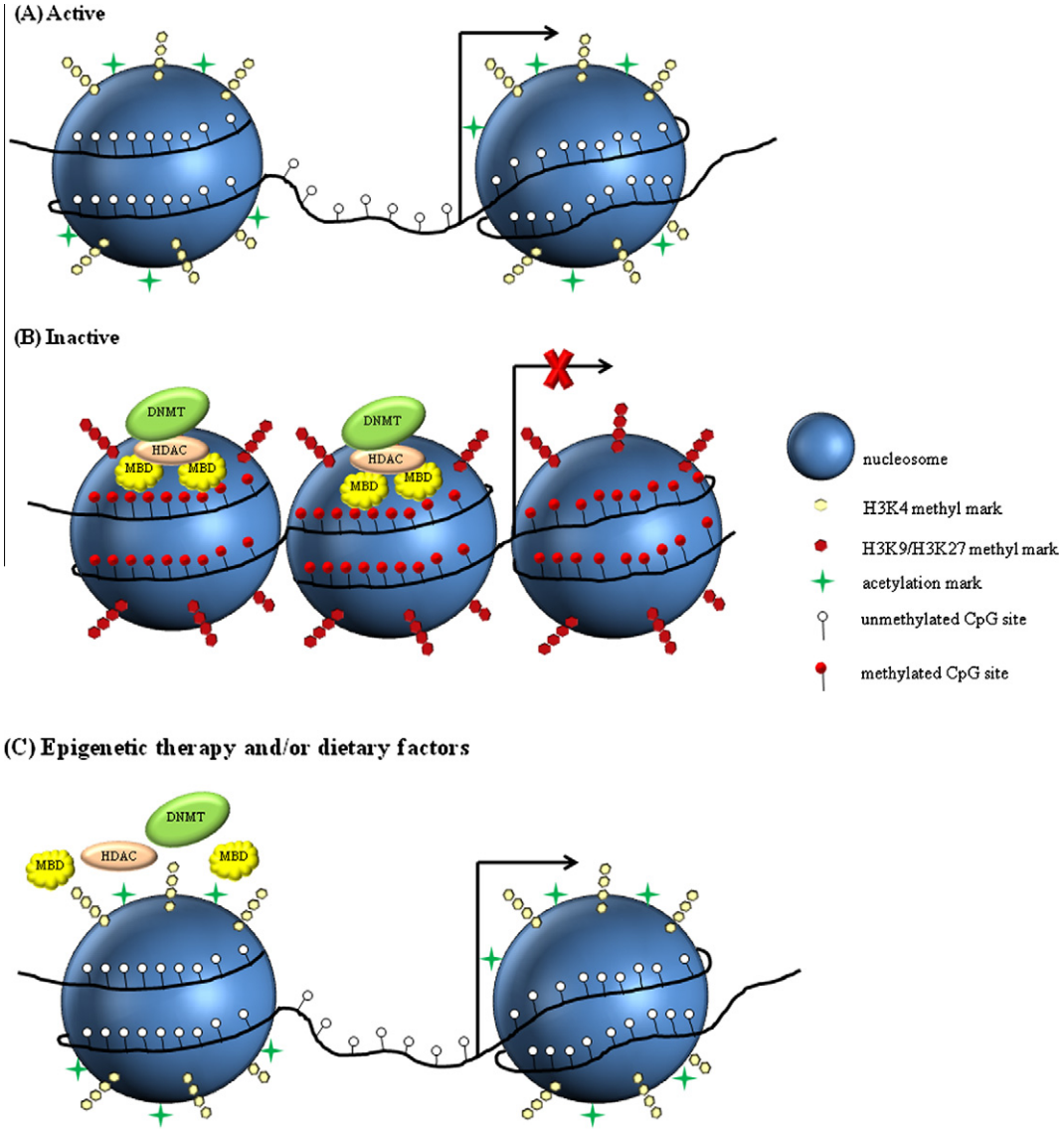

Fig. 1. Simplified diagram shows the epigenetic patterns in promoters of active and inactive genes, and epigenetic patterns of inactive genes affected by epigenetic therapy and/or dietary factors. (A) Promoters of active genes are often associated with unmethylated CpG sites (white circle), acetylation of histone (green cross), and methylation of lysine 4 on histone H3 (H3K4) (yellow hexagon), and are absence of a nucleosome (blue sphere). This configuration favors the access of proteins that activate transcription. (B) During carcinogenesis, CpG sites on the promoters of genes, frequently tumor suppressor genes, are methylated (red circle). MBD mediates transcriptional repression through binding to methylated CpG sites and interacting with HDAC and DNMT. In addition, promoters of inactive genes are associated with methylation of lysine 9 or 27 on histone H3 (H3K9 or H3K27) (red hexagon) and a nucleosome. This pattern renders the chromatin inaccessibility [3,11]. (C) Epigenetic therapy and/or dietary factors decrease DNMT, HDAC, and MBD, and increase acetylation of histones and methyl mark on H3K4 in the promoters of inactive genes. The chromatin might become more accessible to the transcription factors which then activate transcription.

suppression (e.g. BRCA1, VHL), tissue remodeling (e.g. TIMP3, E-cadherin), and hormone receptor (e.g. ESR1, ESR2) [6]. Summarizing results from studies on the correlation between the position of the methylation within a given gene and gene expression indicates that methylation degree within and/or around the promoter region is negatively associated with gene expression level [7,8]. Dose hypermethylation alone cause gene silencing? Studies have shown that DNA methylation may not initiate gene silencing and itself alone does not directly repress transcription. The constitution of chromatin surrounding a hypermethylated gene promoter contributes to the functional state of a gene [8,9]. Chromatins are composed of nucleosomes which contain histone proteins and are winded by DNA. Nucleosomes associated with active and non-methylated gene promoters are normally widely and irregularly spaced with acetylated core histone which favors the access of proteins that activate transcription. In contrast, nucleosomes are tightly and regularly spaced around heavily methylated gene promoters and contain de-acetylated histones [8,9]. This indicates that histone acetylases (HATs) and histone deacetylases (HDACs) are associated with active and silent state of genes, respectively [8,9]. In addition to acetylation, active genes are often associated with methylation of lysine 4 on the core histone H3. The promoters of silenced genes are often marked by methylation of lysine 9 or 27 on histone H3 [8,9]. Although only discovered relatively recently, methyl-CpG-binding domain (MBD) family has been shown to possess a significant role in controlling gene expression. The study on the profile of MBD occupancy of hypermethylated promoter CpG islands of tumor suppressor genes in human cancers indicates