Available online at www.sciencedirect.com
ScienceDirect
Mutation Research 618 (2007) 163–174
Fundamental and Molecular Mechanisms of Mutagenesis
www.elsevier.com/locate/molmut
Community address: www.elsevier.com/locate/mutres

Connections between epigenetic gene silencing and human disease

Timothy J. Moss, Lori L. Wallrath *

Department of Biochemistry, 3136 MERF, University of Iowa, Iowa City, IA 52242, United States

Received 19 May 2006; accepted 25 May 2006
Available online 21 January 2007

Abstract

Alterations in epigenetic gene regulation are associated with human disease. Here, we discuss connections between DNA methylation and histone methylation, providing examples in which defects in these processes are linked with disease. Mutations in genes encoding DNA methyltransferases and proteins that bind methylated cytosine residues cause changes in gene expression and alterations in the patterns of DNA methylation. These changes are associated with cancer and congenital diseases due to defects in imprinting. Gene expression is also controlled through histone methylation. Altered levels of methyltransferases that modify lysine 27 of histone H3 (K27H3) and lysine 9 of histone H3 (K9H3) correlate with changes in Rb signaling and disruption of the cell cycle in cancer cells. The K27H3 mark recruits a Polycomb complex involved in regulating stem cell pluripotency, silencing of developmentally regulated genes, and controlling cancer progression. The K9H3 methyl mark recruits HP1, a structural protein that plays a role in heterochromatin formation, gene silencing, and viral latency. Cells exhibiting altered levels of HP1 are predicted to show a loss of silencing at genes regulating cancer progression. Gene silencing through K27H3 and K9H3 can involve histone deacetylation and DNA methylation, suggesting cross talk between epigenetic silencing systems through direct interactions among the various players. The reversible nature of these epigenetic modifications offers therapeutic possibilities for a wide spectrum of disease.

Keywords: Chromatin; DNA methylation; Epigenetic gene silencing; Histone methylation; Human disease

1. DNA methylation

Altered gene expression can play a causal role in human disease. In many cases, altered expression results from genetic lesions within the gene or regulatory sequences. However, in some cases genetic lesions are absent from the locus. In such instances, aberrant epigenetic modifications of the chromatin surrounding the gene are the cause of altered expression. There are two major epigenetic gene silencing mechanisms that account for a growing number of diseases: cytosine DNA methylation and covalent histone modification.

The 5′ cytosine of CpG dinucleotides within mammalian genomes can be methylated by *de novo* DNA methyltransferases such as DNMT3A and DNMT3B [1]. Maintenance of DNA methylation is performed by DNMT1, utilizing hemimethylated DNA as a substrate. This provides a mechanism to propagate the epigenetic mark following DNA replication. The methyl groups serve as docking sites for gene silencing proteins [2]. In general, DNA methylation correlates with increased chromatin condensation and gene silencing [1].

There are several ways in which altered patterns of DNA methylation lead to disease (Table 1). CpG

* Corresponding author. Tel.: +1 319 335 7920; fax: +1 319 384 4770.
E-mail address: lori-wallrath@uiowa.edu (L.L. Wallrath).

0027-5107/$ – see front matter © 2007 Elsevier B.V. All rights reserved.
doi:10.1016/j.mrfmmm.2006.05.038

Table 1
Gene silencing proteins and disease

Protein	Cellular defect/disease	References
DNMT1	Developmental abnormalities	[110–112]
	Igf2 imprinting	[9]
	Colon cancer	[113–115]
	Lymphoma	[116–118]
	Pancreatic cancer	[119]
DNMT3B	Developmental abnormalities	[120]
	ICF	[1,121–123]
	Bladder cancer	[124]
	Breast cancer	[124,125] [a]
	Colon cancer	[124]
	Hepatocellular carcinoma	[126,127] [a]
	Lung cancer	[124,128,129] [a]
MeCP2	Chromosome instability/cell cycle defects	[49,54,55,57,130]
	Breast cancer	[131]
	Rett syndrome	[132,133], RETTBase
EZH2	Cell cycle defects	[35–37]
	Barrett's esophagus	[134]
	Bladder cancer	[135,136]
	Breast cancer	[41,42,45,137]
	Colorectal cancer	[138]
	Melanoma	[137]
	Myeloma/lymphoma	[29,43,44,46,47,139–141]
	Hepatocellular carcinoma	[142]
	Prostate cancer	[34,39,40,137]
	Wilms tumor	[143]
Suv39h1	Blood cell defects (RBC and WBC)	[54,56,59]
	Chromosome instability/cell cycle defects	[49,54,55,57] [130]
	Chromosome instability	[68–73,75–77]
HP1	Breast cancer	[78,81,82,144]
	Medulloblastoma	[86]
	Papillary thyroid carcinoma	[85]
	Viral latency	[87–92]

[a] Disease associated with polymorphisms.

dinucleotides are generally methylated in normal cells, with the exception of hypomethylation at CpG "islands" located upstream of many active genes [3]. In contrast, cancer cells exhibit a global hypomethylation and CpG island hypermethylation [3]. This shift in the pattern of DNA methylation frequently results in inappropriate silencing of genes, especially tumor suppressor genes, leading to numerous types of cancer. For example, expression of the serine protease inhibitor family member *maspin* is reduced due to methylation of promoter sequences in many advanced forms of cancer [4–6].

Alterations in methylation patterns are responsible for several congenital diseases that affect growth through the misregulation of imprinted genes. Mammalian genomes contain dispersed clusters of genes in which the expression state of each allele is determined by the parent of origin [7]. Transcription within these clusters is regulated by Imprinting Centers (ICRs), DNA regions that are typically 1–2 kb in size and enriched with CpG dinucleotides [8]. ICRs exhibit allele-specific DNA methylation and histone modifications. An ICR positioned between the insulin-like growth factor *IGF2* and *H19* genes is methylated only on the paternal allele, presumably by DNMT1 [9]. This methylation blocks the association of the zinc finger protein CTCF [10,11]. On the unmethylated maternally derived allele, ICR is bound by CTCF, which functions as an insulator by blocking interactions between *IGF2* enhancers located upstream of the *H19* gene. Altered expression of *IGF2* due to changes in the imprinted status at ICR result in two diseases with different clinical characteristics, Beckwith–Weidemann syndrome (BWS, OMIM I30650) and Silver–Russel syndrome (SRS, OMIM 180860) [7] (Table 1). BWS is primarily identified by macroglossia, umbilical abnormalities and gigantism. In a subset of BWS individuals, DNA methylation at the ICR occurs on both the maternal and paternal alleles, resulting in loss of *H19* expression and activation of *IGF2* on both alleles. SRS is identified by low birth weight, slow postnatal growth, characteristic facial abnormalities and body asymmetry. In a subset of SRS individuals, DNA methylation does not occur within the ICR on either allele, resulting in the expression of *H19* from both alleles and complete loss of *IGF2* expression.

In addition to alterations in the patterns of DNA methylation, loss of DNA methyl transferase also leads to disease (Table 1). Immunodeficiency-centromeric instability-facial anomalies (ICF, OMIM 24860) is an autosomal recessive disorder caused by defects within the catalytic domain of DNMT3B [1]. Phenotypes of ICF include instability of chromosomes 1, 9 and 16, which are enriched for pericentric satellite II and III sequences containing CpG dinucleotides. In addition, ICF is associated with immune system malfunctions, facial abnormalities, and short life expectancy. Given that ICF individuals lack the function of a *de novo* DNA methyltransferase, it was anticipated that changes in patterns of DNA methylation would lead to alterations in gene regulation. Expression profiling studies showed alterations in transcription, as expected. How-