Biochimica et Biophysica Acta 1815 (2011) 75–89

Contents lists available at ScienceDirect

Biochimica et Biophysica Acta

journal homepage: www.elsevier.com/locate/bbacan

Review

Histone lysine methylation and demethylation pathways in cancer

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ARTICLE INFO

Article history:
Received 20 August 2010
Received in revised form 6 October 2010
Accepted 7 October 2010
Available online 15 October 2010

Keywords:
Histone methylation
Menin
Cancer
Epigenetics
Epidrugs
Chromatin

ABSTRACT

The genetic changes leading to the development of human cancer are accompanied by alterations in the structure and modification status of chromatin, which represent powerful regulatory mechanisms for gene expression and genome stability. These epigenetic alterations have sparked interest into deciphering the regulatory pathways and function of post-translational modifications of histones during the initiation and progression of cancer. In this review we describe and summarize the current knowledge of several histone lysine methyltransferase and demethylase pathways relevant to cancer. Mechanistic insight into histone modifications will pave the way for the development and therapeutic application of "epidrugs" in cancer.

Contents

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0304-419X/$ – see front matter
doi:10.1016/j.bbcan.2010.10.002

1. Introduction

Genetic and epigenetic alterations are key features of cancer leading to aberrant gene functions and changes in gene expression and genome stability. In contrast to genetic lesions, epigenetic changes in chromatin are biochemically reversible and involve changes in structure and function through post-translational modifications of histone proteins. This justifies the interest into deciphering the regulatory pathways involved in establishing and maintaining chromatin structures in normal and cancerous cells.

Chromatin is composed of repeating units of nucleosomes, which consist of ~146 basepairs of DNA wrapped around an octamer comprised of two copies of the core histone proteins (H3, H4, H2A and H2B). Incorporation of variant histones like CENP-A or macroH2A results in specialized nucleosomes linked in chromatin structures like centromeres or heterochromatin. Nucleosomes are separated by linker DNA of variable lengths, which can be bound by histone H1 to form the 30-nm fiber in order to establish higher-order chromatin compaction. In cells chromatin can exist in either an open or a closed configuration with respect to its accessibility for nuclear proteins. Regulation of this involves what has been called "epigenetic" mechanisms, including DNA methylation, post-translational histone modifications, nucleosome remodeling and non-coding RNAs. Here we use the definition of epigenetics as "stably heritable phenotypes resulting from changes in chromosomes without alterations in the primary DNA sequence" [1].

DNA methylation in eukaryotes occurs by the covalent modification of cytosine residues in CpG dinucleotides and this provides a stable gene silencing mechanism by either preventing or promoting recruitment of regulatory proteins to DNA. In the human genome, CpG dinucleotides are concentrated in short CpG-rich DNA stretches referred to as "CpG islands" [2]. The majority of human gene promoters (50–70%) are embedded within CpG islands [3] and methylation of such islands correlates with transcriptional repression. CpG methylation patterns are frequently altered in tumor cells and an increased methylation contributes to promoter inactivation of tumor suppressor genes.

The core histone proteins are subjected to a variety of post-translational modifications in both their unstructured N-terminal tails and their globular domains. This involves methylation of lysine and arginine residues, acetylation, ubiquitylation and SUMOylation of lysines and phosphorylation of serine and threonines [4]. Whereas lysine acetylation is usually correlated with transcription activation, lysine methylation is associated to transcription activation or repression depending on the residue and degree of methylation. For example, lysine can be in mono-, di- or trimethylated forms. Generally, methylation of histone H3 at lysine residues 9 or 27 (H3K9 or H3K27) or histone H4 at lysine 20 (H4K20) is associated with gene silencing. In contrast, H3K4, H3K36 and H3K79 methylation correlates with gene activity. Methylation of H3K4 by trithorax group (TrxG) family members is most often associated with positive regulation of gene expression, whereas H3K27 methylation by polycomb group (PcG) members represses gene expression [5]. TrxG and PcG genes were initially identified as positive and negative epigenetic regulators of homeotic gene expression in *Drosophila melanogaster*. Strikingly, embryonic stem (ES) cells were reported to possess "bivalent domains" of co-existing active (H3K4me3) and repressive (H3K27me3) marks at developmentally essential genes [6]. Subsequently, the combination of the histone variant H2A.Z with PcG proteins was also shown to create specialized chromatin states in ES cells for cell lineage decisions [7]. These examples illustrate collaboration between different pathways to establish unique epigenetic states.

Histone modification patterns are regulated by enzymes that add, remove or read the covalent modifications. Histone acetyltransferases (HATs also called KATs) and histone lysine methyltransferases (KMTs) add acetyl and methyl groups, respectively, and they have been referred to as "writers" of the histone code [8]. Histone deacetylases (HDACs or KDMs) and histone lysine demethylases (KDMs), known as "erasers," remove acetyl and methyl groups, respectively. Another group of proteins, which possess effector domains including plant homeodomain (PHD), tudor, chromo or bromo domains to recognize specific modified residues, are the "readers" of epigenetic information [9]. Interactions are known to occur between DNA methylation machinery and histone modifying enzymes, which further enhances the complexity of establishing different chromatin states. Non-covalent mechanisms such as chromatin remodeling and replacement of canonical core histones by histone variants are also involved in regulating gene activity. In addition to regulated recruitment of the transcription machinery to the promoter, it has now been shown that chromatin is also involved in promoter-proximal pausing of RNA polymerase II and its release into productive elongation by factors like the P-TEFb kinase [10,11].

The interplay of these mechanisms creates an "epigenetic landscape" which regulates gene expression. This well-balanced transcriptional state of normal cells is changed in most types of cancer cells by altered expression and/or altered function through gene fusions of the writers, readers and the erasers of epigenetic marks. However, as opposed to these genetic lesions, the resultant epigenetic changes are potentially reversible. Efforts are on to develop small molecules coined as "epidrugs" to provide targeted molecular strategies to reverse such chromatin aberrations.

In this review we will discuss on relevance of histone lysine methylation and the associated proteins in the development of cancer. We will provide an overview of several histone methylation pathways and we mention the progress in developing "epidrugs" targeting histone modifications.

2. Distribution of histone lysine methylations in normal cells and in cancer

Next-generation DNA sequencing technologies allowed determining the genome-wide distribution of histone methylations in mammals [12]. This has revealed that H3K4me3 and H3K4me2, for example, are highly enriched at transcriptionally competent or active gene promoters. Mono-methylated H3K4 on the other hand is associated with gene enhancers. Several marks are associated with the transcribed region of active genes and these include H3K9me1, H3K27me1, H3K36me3, H3K79me2/3 and H2BK5me1. H3K27me3 is found at transcriptionally repressed promoters and it displays a broader pattern than H3K4me3. Silent pericentric heterochromatin is marked by H3K9me3. Histone methylation patterns are established through a variety of mechanisms involving interaction of the respective KMT complexes with gene-specific transcription factors, with modified chromatin, with the elongating form of RNA polymerase II enzyme or through direct binding to specific DNA sequences. In