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Review

The role of epigenetics in malignant pleural mesothelioma

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ABSTRACT

Malignant pleural mesothelioma (MPM) is an almost invariably fatal cancer of the pleura due to asbestos exposure. Increasing evidence indicates that unresponsiveness to chemotherapy is due to epigenetic errors leading to inadequate gene expression in tumor cells. The availability of compounds that modulate epigenetic modifications, such as histone acetylation or DNA methylation, offers new prospects for treatment of MPM. Here, we review latest findings on epigenetics in mesothelioma and present novel strategies for promising epigenetic therapies.

1. Introduction

Malignant pleural mesothelioma (MPM) is a cancer associated with asbestos exposure [1,2]. Incidence of MPM is expected to increase significantly in upcoming years with a peak around 2018 in Western Europe [3]. In the United States, Great Britain and Japan, over 5000 cases of MPM occur annually [4–6]. Although the etiology of MPM is well known, therapeutic approaches have been disappointing. Available treatments have not proven their ability in significantly prolonging survival in comparison to supportive care. Currently, standard therapy for MPM is still deficient: the possibility of curative surgery is extremely rare. The impact of chemotherapy on the outcome of patients with MPM is still controversial, the median survival being about 8–12 months [7]. The high mortality rate associated with these cancers is mainly due to the lack of efficient screening approach for early detection and to the ineffectiveness of current treatments. Currently, only a single randomized trial has demonstrated an increase of response rate and survival when comparing cisplatin and pemetrexed versus cisplatin alone [8]. Unfortunately, most patients become resistant to this treatment and relapse rapidly. There is no standard regimen for second line treatment, the chemotherapeutic agents used showing only marginal response rates [9–12].

Although genomic alterations are clearly associated with oncogenesis, more recent evidence shows that changes that are not directly indicated in the DNA sequence also play an important role in cancer development. These "epigenetic" modifications affect temporal and spatial control of gene activity required for homeostasis of complex organisms [13]. In fact, epigenetics includes heritable and reversible changes modulating a variety of mechanisms such as RNA elongation, mitosis, DNA replication and repair. By affecting gene activity, epigenetics also plays a major role during tumorigenesis. Knowledge of epigenetics has provided new therapeutic opportunities against cancer, especially those for which current therapies are ineffective such as MPM. In this context, several studies have demonstrated that epigenetics is an important contributor of MPM development and plays a determining role in response to treatment as well. The fact that epigenetic modifications, unlike genetic changes, are potentially reversible opens prospects for novel therapeutic targets. Here, we summarize the current knowledge pertaining to epigenetic deregulations in MPM and present different models of promising epigenetic therapies.

2. The role of epigenetics in cancer development

The basic unit of chromatin is the nucleosome which consists of 146 bp of DNA wrapped around an octamer of histones (the core nucleosome). This octamer is composed of two molecules of each of the four canonical histone proteins (i.e. H2A, H2B, H3, and H4). Histone H1 adds an additional torsion to the DNA around the core nucleosome [14]. Histones are small and highly basic proteins that contain a globular C-terminal domain and a flexible N-terminal tail. The globular domains of the histones form the nucleosome core while the N-terminal tails of the histones are involved in

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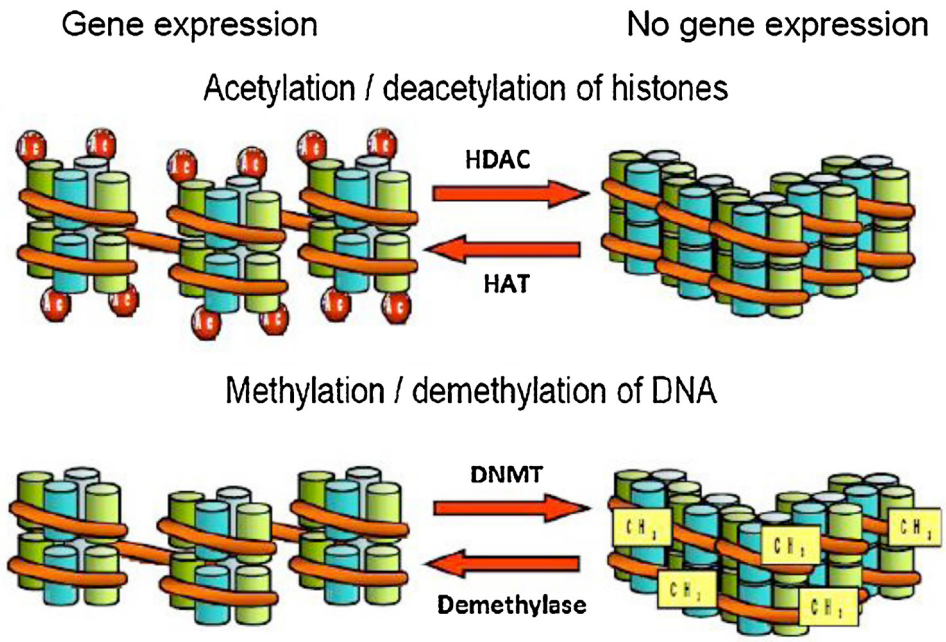

Fig. 1. Lysine acetylation and DNA methylation modulate chromatin compaction and gene expression. HDAC (histone deacetylase), HAT (histone acetyltransferase), DNMT (DNA methyltransferase).

inter-nucleosomal interactions and recruitment of non-histone proteins to chromatin [15]. These N-terminal histone tails can be modified post-translationally for example through acetylation or methylation (Fig. 1). The second main epigenetic modification, cytosine methylation, directly involves the DNA molecule.

At the DNA level, methylation takes place at the carbon-5 position of cytosine residues within DNA stretches containing CpG. These dinucleotides are not equivalently distributed throughout the genome but are essentially concentrated in gene promoters (40–60%). These regions of at least 200 bp and up to several kb in length are called CpG islands. In normal cells, most CpG islands are usually unmethylated while the rest of the genome is methylated [16,17]. DNA methylation leads to gene silencing by the modulation of the binding of regulatory proteins to DNA. In normal cells, CpG island methylation ensures mono-allelic expression, X-chromosome inactivation in females and extinction of repetitive elements and germ-line genes (e.g. MAGE) [18]. Inappropriate DNA methylation such as hypermethylation of tumor suppressor genes, hypomethylation of oncogenes and hypomethylation of repetitive elements can lead to oncogenesis. DNA methylation is mediated by DNA methyltransferases (DNMTs). Three major DNMTs (DNMT1, DNMT3a and DNMT3b) involved in DNA methylation use S-adenosyl-methionine as the methyl donor [13]. DNMT1 permits mitotic inheritance of methylated DNA bases and has therefore a preference for hemimethylated DNA [19]. In contrast, DNMT3a and DNMT3b modulate *de novo* methylation of unmethylated sites [20].

Besides DNA methylation, histones and their post-translational modifications affect chromatin structure. Several modifications may occur at the histone tails but also at the level of their globular domains. Modifications such as lysine acetylation and methylation affect compaction of chromatin and regulate interaction of histones with their partners, thereby regulating gene expression and DNA replication.

Histone acetylation weakens the interaction between histones and DNA by neutralizing the positive charge of lysines. Histone acetylation renders the DNA more accessible for the transcriptional machinery and acts as a docking site for transcriptional modulating proteins. Therefore, enhanced gene expression has been associated with histone acetylation of H3K9, H3K14, H3K18, H3K23, H4K5, H4K8, H4K12 and H4K16 [21–27]. In this nomeclature, H3 and H4 correspond to the histone, K to a lysine residue associated to its position starting from the aminoterminus. Histone acetylation is mediated by histone acetyltransferases (HATs) whereas the opposite reaction is catalyzed by histone deacetylases (HDACs) [28]. HATs are classified in different families (GNAT, MYST and CBP/P300) based on the presence of highly conserved structures [29]. Eighteen human HDACs are classified according to their sequence similarities [30]. HDACs belonging to classes I, II and IV are zinc-dependent whereas members of class III are NAD^+-dependent. While acetylation affects the electrostatic properties of the nucleosome, histone methylation at lysine or arginine residues does not alter the charge of amino acids but provides specific binding platforms for chromatin-associated proteins. Histone methylation promotes transcriptional activation or repression through the recruitment of co-activators or co-repressors such as HP1 [31]. The residue on which methylation occurs and the degree of methylation (mono-, di-, or trimethylation) determine the effect of histone methylation [24,32,33].

Besides methylation and acetylation, histone tails can undergo a series of other posttranslational modifications such as phosphorylation, sumoylation, ADP-ribosylation, biotinylation, proline isomerization and ubiquitination. Although less characterized, these modifications regulate essential functions such as for example chromosomal condensation and segregation through phosphorylation of H1 and H3 [34]. These modifications are frequently interdependent as illustrated by the required ubiquitination of H2B for methylation of H3K79 [35].

As outlined above, DNA methylation and histone post-translational modifications are interlinked processes that act in a coordinated manner to determine the transcriptional status of a specific gene. Thereby, epigenetic abnormalities such as hypomethylation can affect cell fate and lead to transformation. In particular, cancer cells are characterized by a genome-wide hypomethylation and a site-specific hypermethylation [36,37]. Hypomethylation contributes to cancer development by