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Epigenetic therapy and chemosensitization in solid malignancy

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ABSTRACT

Epigenetic modifications result in dynamic shifts between transcriptionally active and suppressed states. The potentially reversible nature of epigenetic changes underlies the concept of epigenetic therapy, which serves to reprogram cancer cells as opposed to inducing cytotoxicity that occurs with standard chemotherapeutics.

There are numerous enzymes involved in epigenetic changes and each can be potentially targetable. Although many investigations have evaluated the clinical potential of the various epigenetic therapies, currently only histone deacetylase inhibitors and DNA methyltransferase inhibitors are approved for use in specific hematologic malignancies.

Use of epigenetic therapy coincident with cytotoxic or targeted systemic therapy appears to derive a benefit due to chemosensitization. Trials demonstrating efficacy from combination therapy have been performed in various diseases such as NSCLC, ovarian cancer and breast cancer. Furthermore, there are patient subsets in certain solid tumors in which epigenetic therapy provide durable response, such as patients with NSCLC and specific hypermethylation patterns. The encouraging results from combination therapy identified in these trials built upon prior investigations and have provided a foundation for ensuing trials seeking to evaluate epigenetic therapy.

Introduction

The remarkable diversity of malignant processes underlies the difficulty in elucidating pathophysiology of and treatment for cancer. As eloquently outlined by Hanahan and Weinberg, a number of traits are acquired in the transformation from normal cell to neoplastic process, including sustained growth promoting signaling, circumventing apoptosis, immune evasion, and suppression of tumor suppressor genes [1]. These changes may occur via somatic mutations; alternatively, they can arise from epigenetic modification. For instance, cancer cells can achieve sustained proliferative stimulation via mutation in phosphatase and tensin homolog (*PTEN*), resulting in loss of function and amplification of PI3K signaling; similarly, PTEN expression can be inhibited by promoter methylation, which is a form of epigenetic modification [1].

Initially, epigenetic changes were found to be integral to malignant processes through a series of gene expression and DNA methylation studies [2]. Many of the early studies did not establish mechanism or pathways, but did identify a potential correlation between epigenetic modifications and cancer. With improved understanding of epigenetics, it has become clear that genetic and epigenetic changes are concomitantly involved in cancer initiation, promotion and progression. Affirming this concept is the fact that there have been identified a number of genetic lesions in epigenetic regulators in nearly all tumor types [3,4]. The ensuing aberrant signaling from these epigenetic regulators can then further promote gene expression alterations through modification of histone structure.

Epigenetics encompasses the heritable phenotype that arises from covalent modifications in histones and DNA without alterations of the DNA sequence itself [5,6]. Signals that initiate epigenetic changes may be an environmental cue, internal stimuli or developmental signals. Following the initial input, signal transduction incites a protein or noncoding RNA to establish chromatin interaction at a specific location, followed by a sustained chromatin state [5]. The chromatin-DNA interaction influences chromatin configuration; the presence of DNA in nucleosome-depleted regions is associated with gene expression while tightly bound DNA in the nucleosome structure leads to gene repression [7,8]. Nucleosomes consist of DNA wrapped around eight core histone proteins (2 each of H2A, H2B, H3 and H4), and post-translational modification of these core histones includes histone acetylation, methylation, ubiquitination, sumoylation, and phosphorylation; each can change the nucleosome structure, resulting

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in modulation of DNA gene expression (see Fig. 1) [8–11]. Additional changes promoting gene transcription or gene repression arise from DNA methylation and the collective set of enzymes, which regulates open and closed chromatin conformation. Together, these changes allow regulation of cellular physiology such as transcription, DNA damage repair, DNA replication, genomic imprinting and X chromosome inactivation [6,11].

Enhanced understanding of epigenetic processes over the last several decades has identified a role for epigenetics in normal cellular mechanisms but also a significant role in cancer. This review encompasses epigenetics in the context of various malignant processes and therapeutic targets. Additionally, there have been an increasing number of clinical trials evaluating epigenetic therapy; earlier trials provided lessons for subsequent studies, and concepts such as combination therapy and chemosensitization have also arose. Finally, a discussion of future directions in epigenetics will be included.

Epigenetics and malignancy

Epigenetic gene silencing is a common feature in tumor cells and typically arises from DNA hypermethylation at tumor suppressor genes. The targeted gene regulatory regions (promoters or enhancers) undergo DNA hypermethylation at cytosine residues within CpG-islands [12]. In general, CpG sequences are dispersed throughout the genome with relatively low frequency and are typically heavily methylated. In contrast, CpG-islands contain a high frequency of the CpG dinucleotide; these islands are present in gene promoter regions and are unmethylated to allow gene expression. However, in malignant processes, enzymes including DNA methyltransferase (DNMT) can inhibit tumor suppressor gene expression via CpG island hypermethylation, such as hypermethylation of the *MLH1* promoter in the sporadic form of microsatellite unstable colorectal cancer [13]. Regions of DNA methylation are interpreted by methyl-CpG binding proteins (MBP), which promote a transcriptionally inert chromatin environment via recruitment of histone-modification genes such as histone deacetylase (HDAC) or histone methyltransferase (HMT) containing complexes [13–15]. Therefore, regions of CpG island methylation are also characterized by histone hypoacetylation (histones H3 and H4) and histone methylation (H3K9-me) [6]. The polycomb repressor complexes (PRC), PRC1 and PRC2, are also critical for numerous cellular processes and function to silence transcription via H3K27 methylation (PRC2) and DNA condensation (PRC1) [10,11]. Interestingly, not all methylation events promote a transcriptionally inert state; while H3K9-me3 is associated with compact heterochromatin, trimethylation of lysine 4 in histone 3 (H3K4me3) promotes induction of gene expression [12]. Furthermore, certain signatures are associated with both an activating and repressive pattern. In embryonic stem cells, concomitant methylation of histone 3 at lysine 4 (H3K4me3) and lysine 27 (H3K27) promotes a bivalent domain in which gene expression is suppressed but readily able to switch to an activated state [11]. Histone 3 tail acetylation (H3K14Ac and H3K27Ac), carried out by histone lysine (K) acetyltransferases (HAT, also known as KAT), neutralizes the positively charged lysine and weakens the lysine-DNA interaction, thereby promoting a transcriptionally active chromatin structure [14]. Other enzymes involved in histone and DNA modification include, kinases, histone demethylases (HDM), ten eleven translocation protein 1–3 and phosphatases. Focused studies have also elucidated a role for microRNAs (miRNAs) in facilitating epigenetic signaling. These small, non-coding RNAs exist as post-transcriptional regulators of gene expression and fall under the category of epigenetic regulators given their modification of gene expression without alteration of DNA sequence [10]. For instance, among the miRNAs evaluated, miRNA-29 and miR-101 have been associated with gene promoter hypermethylation [7].

The combination of DNA methylation at promoter or enhancer regions, histone modifications and non-coding RNA interactions collectively determine gene expression [11]. Compared to changes in the linear DNA sequence, shifts between transcriptionally active and suppressed states from epigenetic modifications are heritable in somatic cells but potentially reversible. This concept drives the aim of epigenetic therapy, which serves to reprogram cancer cells as opposed to inducing cytotoxicity that occurs with standard chemotherapeutics. Therapies targeting epigenetic changes have been developed in order to reverse or block the deviant epigenetic modifications that occur in tumor cells. These agents are targeted to the various enzymes responsible for epigenetic modification and gene expression such as DNMTs, KATs, HDACs, HMTs, HDMs, non-coding RNAs and kinases; among them include 5-azacitidine

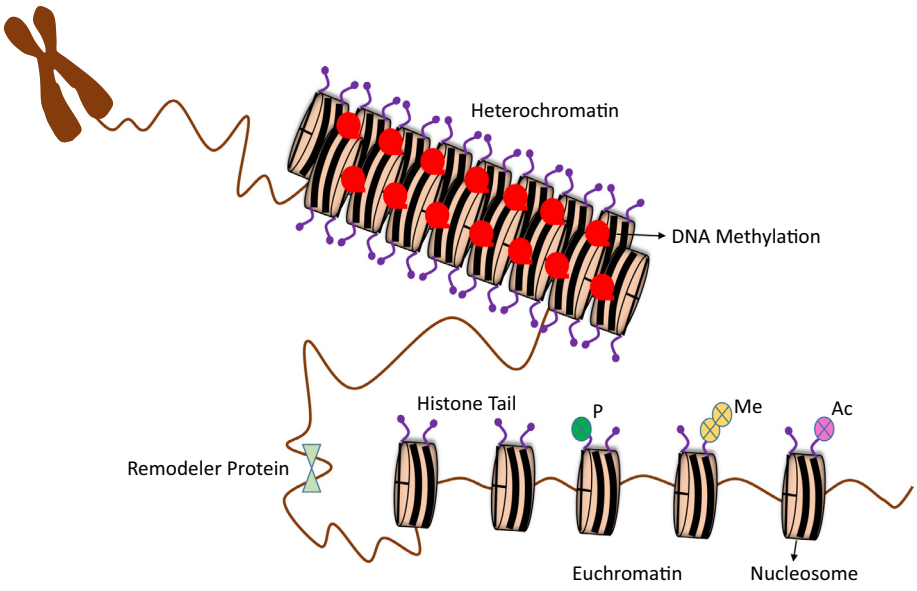

Fig. 1. The epigenome topography.