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Review

Development and classes of epigenetic drugs for cancer

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ABSTRACT

Emerging evidence supports an important, etiologic role for epigenetic modifications in cancer. Various post translational modifications of histone proteins together with DNA methylation constitute an 'epigenetic code' regulating the transcriptional status of the cell and aberrant writing and/or interpretation of the code can contribute to a dysregulated, hyperproliferative state. In some cases, epigenetic deregulation has also been reported to result in tumor initiation. The discovery of somatic mutations in some chromatin binding proteins associated with subtypes of lymphomas and the ability to regulate expression of proto oncogenes such as Myc has spurred the development of specific small molecule modulators of histone binding proteins. Several of these compounds have entered clinical development for the treatment of heme malignancies. This review summarizes progress in the discovery and advancement of epigenetic therapeutics for cancer and provides a perspective for future development.

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1. Introduction

Significant advances have recently been made in the understanding and recognition of the important contribution of epigenetic factors to the malignant phenotype. More routine molecular profiling of various tumors driven by advances in technologies such as next generation sequencing has allowed for the identification of somatic alterations highlighting epigenetic deregulation as a feature of many cancers (see review by Omar Abdel-Wahab [133]). Reflecting this progress has been an increased interest in developing therapeutics targeting specific

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chromatin associated proteins in much the same way as the successful development of currently used targeted protein kinase inhibitors. Clearly, the analogy can be readily extended to include the possibility of developing 'personalized epigenetic medicines' tailored to a patient's tumor profile and accompanied by both a drug and a molecular diagnostic for patient selection. In this context, it is particularly exciting to note the recent advancement of multiple such potential therapies to clinical evaluation [1,2]. The increased availability not only of clinical agents but also selective, cell permeable 'tool' compounds pioneered by the Structural Genomics Consortium [3] continues to extend and guide research efforts in many laboratories, promising to reveal additional insights to spur the discovery of novel drugs. While not the subject of this Review, it is also worth mentioning the potential for applying epigenetic therapies in non-oncology indications such as neurology [4], metabolism [5], and infectious diseases [6] although critically, an understanding of epigenetic pathways in these processes is only now beginning to emerge.

2. Epigenetic modifications and the 'histone code'

The uncoiled length of nuclear DNA vastly exceeds the size of the cell and therefore exists in a highly compacted form tightly wrapped around the histone proteins H2A, H2B, H3 and H4 in the form of nucleosomes [7]. High resolution X-ray crystal structures of nucleosomes have revealed the presence of short chains ('tails') of ~30 amino acids protruding from the histones [8,9] and subject to various post translational modifications (PTMs) including acetylation, methylation, phosphorylation, ADP-ribosylation, etc. [10]. These PTMs serve to induce local changes in chromatin structure allowing for selective access of transcriptional machinery to the DNA. Importantly, the PTMs are highly dynamic and respond to a variety of signals suggesting a mechanism for the cell to sense and respond to its environment. In addition to histone PTMs, methylation of DNA at cytosine C5 constitutes a second major epigenetic modification and is normally associated with gene silencing (see the review by Hiromu Suzuki [134]). Together, DNA methylation and histone PTMs are both tightly regulated to control the overall transcriptional state of the cell.

Within the histone tails, lysine and arginine residues are the major sites for modification and typically, reversible acetylation and methylation of the basic side chains of these amino acids are common. Indeed, the most recent drug discovery efforts have largely focused on modulating the introduction, removal or interpretation of these modifications. Nonetheless, as mentioned above, phosphorylation, ubiquitination, SUMOylation and crotonylation of serine and threonine residues amongst other modifications have also been observed and affect transcription and/or the cell cycle (e.g. phosphorylation of histone H3 at serine 10 by the Aurora kinases is critical during mitosis, [11]).

Enzymatic acetylation and methylation of histone lysine and arginine amino groups is catalyzed by histone acetyl transferases (HATs) and protein methyl transferases (PMTs) respectively with the latter further subdivided to lysine (KMTs) and arginine (RMTs) targeting proteins [12]. Reversal of the modification is carried out by corresponding deacetylases (HDACs) and lysine/arginine demethylases (K/RDMs). Similarly, *de novo* DNA methylation is accomplished by the methyltransferases DNMT3A and DNMT3B with a second related protein, DNMT1 being responsible for methylation of hemimethylated DNA [13]. Collectively, the dynamic introduction, removal and combinatorial interpretation of the various histone PTMs and DNA methylation has been referred to as the writing, erasing and reading respectively of an 'epigenetic code' [14] by analogy to the more familiar genetic code. Small molecule inhibitors of some of the enzymes and PTM 'reader' proteins have been developed (Table 1) and advanced to clinical studies for a variety of tumor types [15–17]. A number of these will be described below.

3. First generation epigenetic inhibitors

3.1. DNA methyltransferase inhibitors

As mentioned above, the DNA methyltransferases DNMT1, DNMT3A and DNMT3B catalyze the transfer of a methyl group from the methyl donor S-adenosylmethionine (SAM) to the C-5 of cytosine in DNA. In normal cells, the DNMTs play a variety of roles including maintenance of chromosomal stability, silencing of genes, and regulation of embryonic development. In cancer cells, hypermethylation at CpG islands can lead to inactivation of several important tumor suppressor genes including p16 [18] and in order to reverse this epigenetic silencing, small molecule inhibition of DNMT has been pursued as a therapy for several forms of cancer [19,20].

Of the three catalytically active DNA methyltransferases identified, DNMT1 is the most abundant and maintains methylation during DNA replication while DNMT3A and DMT3B both are responsible for establishing methylation patterns during embryonic development. Studies with conditional ablation have shown loss of DNMT3A in human stem cells leads to the inhibition of differentiation and the hypomethylation of multiple genes [21]. Recently, experiments in mice using conditional knockouts have suggested DNMT3A and DNMT3B may also function as tumor

Table 1
Classes and stages of epigenetic inhibitors.

Class	Preclinical	Clinical	Approved
DNMT	SGI-1027, RG-108, procainamide, epigallocatchin, nanomycin A	Zebularine, SGI-110	Azacitidine, decitabine
HDAC	TFMO derivatives	Entinostat, panobinostat, givonostat, belinostat, mocetinostat, tacedinaline, resminostat, AR-42, Kevetrin	Vorinostat, romidepsin
Histone methyltransferases			
G9a	BIX01294,UNC0321, UNC0638,UNC0642,spiroindolamine		
EZH2	Novartis EI1, UNC-1999, GSK343, EPZ-5687	EPZ-6438, GSK126	
DOT1L	SGC-0946, EPZ-4777	EPZ-5676	
PRMTs	BMS PRMT4		
Histone demethylases			
LSD1	OG-1002, GSK354	Tranylcypromine, ORY-1001, GSK9552	
JmjC	GSK-J1, IOX-1		
Bromodomains	JQ1, IBET151, PF-1, RVX-280	IBET762, CPI-0610, OTX015, TEN-010	
MBTL	UNC-669, UNC-1215, UNC-2533		