

EDITORIAL

Promoting Illiteracy in Epigenetics: An Emerging Therapeutic Strategy

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Beyond the Human Genome

On the 10th anniversary of the announcement of the draft sequence of the 3 billion DNA bases in the genome by the Human Genome Project, there is still a lack of molecular targeted therapies for previously intractable diseases. It has become clear that the genomes within and across species are too similar to explain the diversity of life and the etiology of all diseases, indicating that the underlying DNA sequence is only one component of this problem. Coinciding with the accomplishment of this impressive feat led by the NIH and Celera Genomics, has been the explosion of research defined as “epigenetic”. The term epigenetics was first coined in the 1940s by British embryologist and geneticist Conrad Waddington [1], who was attempting to describe “the interactions of genes with their environment, which brings the phenotype into being”. Since then, this definition has been refined to encompass the study of heritable phenotypic traits that result

from modifications to a chromosome that do not alter the underlying genetic code [2]. An increasing awareness of the importance of the temporal and spatial control over the expression of genes has elevated the study of epigenetics to a torrid pace (Fig. 1). There is even a sequel to the Human Genome Project, the International Human Epigenome Project (IHEP), which was launched in 2010. The IHEP’s goal is to understand the patterns of DNA methylation and post-translational histone modifications that ultimately control access of specific genes to transcriptional machinery.

Epigenetic Therapies Already in the Clinic

The potential for new classes of molecular targeted epigenetic therapies has begun to be realized with FDA-approved inhibitors of histone deacetylases (HDACs) (Vorinostat and Romidepsin) and DNA methyltransferases (DNMTs) (5-azacytidine and 5-aza-2’-deoxycytidine). However, these agents were discovered based on observation of

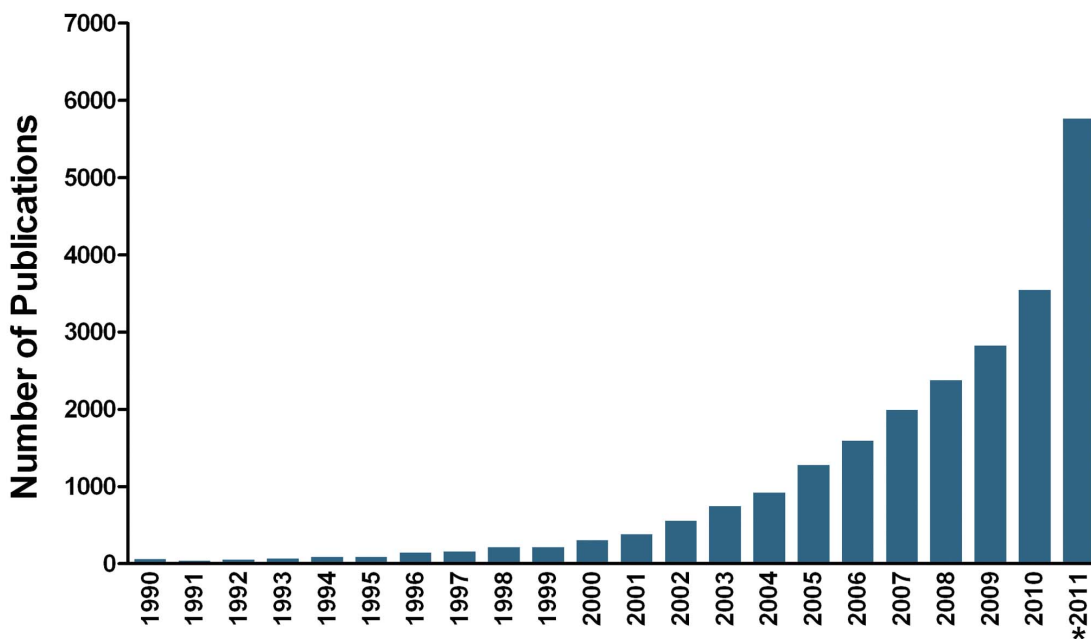


Fig. (1). Epigenetic Research on a Steep Ascent. The search term “epigenetic” was queried by year using the U.S. National Library of Medicine Pubmed search engine. *The number of publications for 2011 is an estimate based on the current pace of publications through February 15th, 2011.

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cell phenotypes and the biochemical targets were discovered several years later. Suberoylanilide hydroxamic acid (SAHA, Vorinostat; approved 2006), the first generation clinical HDAC inhibitor brought to market, was discovered by phe-

notypic screens to be a potent differentiating agent whose molecular targets, the HDACs, were identified shortly thereafter [3-5]. Similarly, the azacytidines (5-azacytidine, Vidaza; approved 2004 and 5-aza-2'-deoxycytidine, Deco-gen; approved 2006) were noted to have anti-proliferative effects *in vitro* on cancer cells in 1964, and the molecular targets, DNA methyltransferases, were determined only 15 years later [6, 7]. These discoveries and their subsequent development into therapeutic agents indicate the potential of epigenetic therapies. As a result target-centric, bottom-up approaches to epigenetic drug discovery have rapidly intensified across both industry and academia. Epigenetic targets are now ubiquitous in drug discovery pipelines and there are now multiple biotechnology companies dedicated to pursuing epigenetic therapies, as highlighted in a recent review by Mack [8].

Histone Methylation: The Next Epigenetic Therapy?

An extensive literature search reveals at least 232 enzymes that are proven or postulated to add or remove histone post-translational modifications (Fig. 2). Given that histone acetylation and DNA methylation have already been exploited with approved therapeutics, this issue of *Current Chemical Genomics* focuses on histone lysine methylation, which is emerging as an attractive target for drug discovery. Amongst histone-modifying enzymes, the lysine and arginine methyltransferases (KMTs and RMTs), and lysine demethylases (KDMs) comprise more than half of the total number, yet there are no inhibitors of these enzymes in clinical studies. Furthermore, a growing body of evidence suggests that genetically driven alteration of their enzymatic activities and specificities drives disease progression. For example, point mutations to the lysine methyltransferase EZH2 that change the product specificity of the PRC2 complex from monomethyl- to trimethyl-lysine have been char-

acterized in a subset of lymphoma patients. As a result, heterozygosity leads to the coordinated activities of mutant and wild-type enzymes in the trimethylation of lysine 27 on histone H3, a notorious mark that is ubiquitous in many cancers [9, 10]. Translocations creating fusion proteins with aberrant activity have also been observed in disease, such as the MLL-partner fusions that result in the mistargeting of H3K79 methylation by DOT1L in childhood leukemias [11] or NSD1-nucleoporin 98 fusions that are associated with acute myeloid leukemia [12]. Recently, overexpression of the lysine methyltransferase SETDB1 was found to accelerate the progression of melanoma in an elegant zebrafish model [13], and similarly, overexpression of the lysine methyltransferases SMYD3 [14] and G9a [15] have been observed in a variety of cancers. In the case of the latter, the recent development of selective, sub-nanomolar inhibitors [16] will enable its investigation as a target for cancer therapy. In addition, the lysine demethylases LSD1 and JARID1B are found to be overexpressed in prostate cancer [17], and inhibitors of LSD1 have shown promise in controlling the proliferation of cancer cells using xenograft models [18]. Ultimately, these examples represent the intersection of genetics and epigenetics, and define a targeted patient population that will enhance the probability of clinical success.

The discovery of potent chemical probes of KMTs and KDMs are a critical first step in the dissection of the biological pathways they regulate and in understanding the consequences of genetically-driven misregulation of their activities. These enzymes appear primed for drug discovery, with a wealth of structural information now available to guide medicinal chemistry efforts, and this is reviewed in this issue by articles from Heightman and Shapira. The readers of lysine methylation, including PHD fingers, MBT domains, Tudor domains, chromodomains, PWWP repeats and WD40 repeats, which may also make interesting drug targets, are

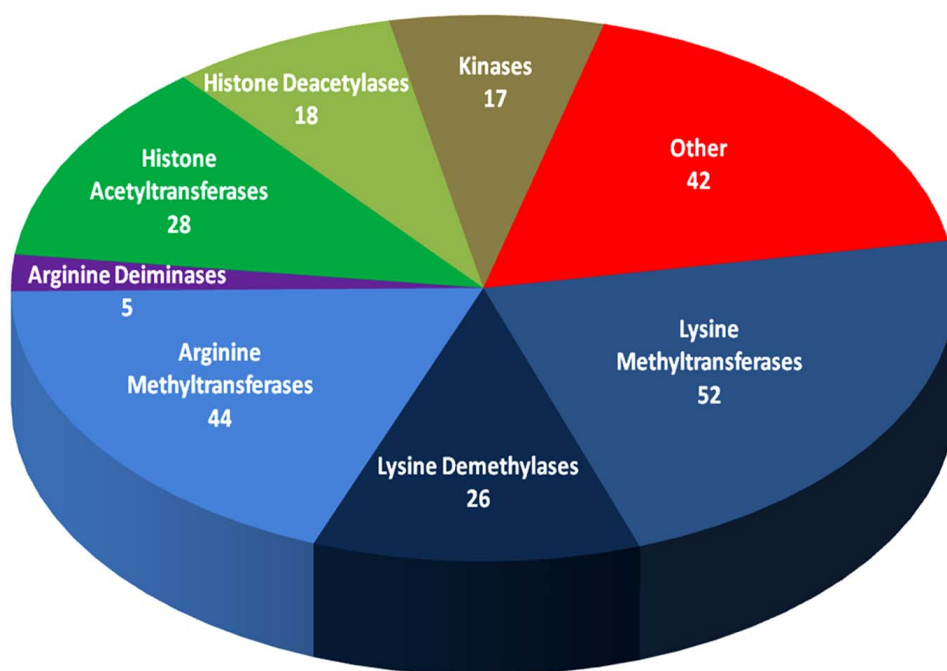


Fig. (2). At least 232 confirmed or putative chromatin-modifying enzymes have been identified. The total number of histone modifying enzymes of each class are indicated. This data was compiled using an extensive search of the current literature. The “Other” category includes ubiquitin ligases, deubiquitinases, SUMO ligases, SUMO isopeptidases and phosphatases.

reviewed by Herold *et al.* The assay technologies that will enable chemical exploration of these targets are quickly evolving and are highlighted by Quinn and Simeonov and Zee *et al.* Finally, pioneering efforts in HTS and medicinal chemistry have indicated that indeed, these enzymes appear chemically tractable, and the current state of chemical matter targeting histone methylation is reviewed by Yost *et al.* and Heightman in this issue.

While it is likely that modulators of histone lysine methylation will yield clinical candidates in the future, the study of histone lysine methylation and its effect on biological processes is still in its relative infancy. It remains to be seen how many enzymes or proteins will make for good therapeutic targets. The integration of current efforts in genomics, chemical biology and drug discovery efforts should begin to deliver greater understanding of the potential of epigenetic targets. The research undertakings and accomplishments reviewed in this issue will be critical in the validation of small molecule modulators of methyl-lysine writers, readers and erasers as first-in-class molecular targeted therapies. These targeted agents should be an improvement over current treatments, and will have a profound impact on patients with unmet medical needs.

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