Boumber and Issa provide a useful review of the development of agents that target the epigenome—primarily DNA methyltransferase (DNMT) inhibitors and histone deacetylase (HDAC) inhibitors. The authors provide a summary of agents approved for clinical use: the DNMT inhibitors azacitidine (Vidaza) and decitabine (Dacogen), and the HDAC inhibitors vorinostat (Zolinza) and romidepsin (Istodax). In addition, they summarize available clinical trial data from a number of novel drugs that target the epigenome. As the authors indicate, this list is selective. There are at least another 12 to 15 “epigenetic drugs” in clinical trials, and many more in various stages of preclinical development.[1,2]

While Boumber and Issa state that HDAC inhibitors lead to activation of genes, several studies have shown that about the same number of genes are up-regulated as are down-regulated by these epigenetic modifying agents.[3] The mechanism of action of the HDAC inhibitors is not well understood.

Both DNMT inhibitors and HDAC inhibitors cause alterations in proteins that regulate cell cycle progression, apoptosis, and other pathways that affect the survival of transformed cells. Choudhary et al[4] identified 3600 acetylated lysines in 1750 proteins; of these acetylated sites, vorinostat altered only about 10%. The proteins whose structure and function were altered by the HDAC inhibitor have a role in many cellular pathways—including DNA damage repair, cell cycle progression immune pathways, cell migration and adhesion, and angiogenesis. These studies and others show that the alterations to gene expression and protein structure that are induced by DNMT and HDAC inhibitors are complex.[5] As Boumber and Issa discuss, gaining a better understanding of the changes that are consequent to the alterations in the structure and function of these proteins should lead to improved strategies for combination therapy with other “targeted” anti-cancer agents. Given the modest efficacy of the DNMT and HDAC inhibitors as monotherapy, particularly for solid tumors, combination therapy is likely to be a more promising path to effective use of these agents.

Developing the most potent inhibitors of DNMT or HDAC on the basis of in vitro assays or in vivo animal studies may not yield the best therapeutic agent. For example, the HDAC inhibitor vorinostat has a moderate binding constant to the HDAC enzymes. Its inhibitory activity is rapidly reversible upon removal of the agent.[6] This may account for vorinostat’s relative selectivity for neoplastic cells—and may explain why normal cells are relatively resistant to HDAC inhibitor–induced cell death. It has been shown that normal cells—but not transformed cells—can repair DNA damage induced by HDAC inhibitors.[7] The failure of cancer cells to repair the damage induced by these inhibitors reflects the fact that the vast majority of transformed cells have multiple gene and protein defects. In a study of 10 samples of colon cancer and 10 samples of breast cancer, over 600 gene mutations were identified in one or more tumors.[8,9] More highly potent HDAC inhibitors currently being developed may have more toxicity than vorinostat.

Understanding the biological activities of the 11 zinc-dependent HDACs and the different members of the DNA Mtase family of enzymes is a work in progress. The development of isoform-selective inhibitors of these enzymes will be useful in dissecting their biological function, and such compounds may prove to be therapeutic agents with more targeted efficacy and possibly fewer undesirable side effects.

Epigenetic targeted therapy is in an early stage of development. Both at the mechanistic level and at the clinical/therapeutic level, much remains to be learned. Which cancers are likely to be responsive? What combination with anti-cancer drugs will enhance the efficacy of the epigenetic drugs? What are the molecular markers that may predict resistance or sensitivity to these drugs? We can anticipate the discovery of many new and, hopefully, better epigenetic drugs. Progress in this area of cancer therapeutics is promising; however, it is also challenging.
Financial Disclosure: Memorial Sloan-Kettering Cancer Center (MSKCC) and Columbia University own the patents on suberoylanilide hydroxamic acid and related histone deacetylase inhibitors, which are licensed exclusively to Merck. Dr. Marks receives royalties from MSKCC related to this license.

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