In this issue of Clinical Cancer Research, Huang and colleagues, characterize the effects of novel histone demethylase inhibitors, either alone or in combination with inhibitors of DNA methyltransferases (DNMTI), on the proliferation and survival of transformed cells (1). A widely accepted view holds that the origins of cancer lie, at least in part, in the silencing of genes responsible for cell death and/or differentiation, a phenomenon that generally stems from perturbations in the transcriptional regulatory machinery. In the broadest sense, silencing of such genes occurs at three fundamentally different but closely interrelated levels. For example, silencing frequently results from DNA methylation at the site of CpG islands by DNA methyltransferases (DNMT; ref. 2). Silencing can also stem from mutations in chromatin remodeling complexes [i.e., nucleosomal remodeling factors (NURF)] such as SWI/SNF. Finally, silencing can result from multiple post-translational covalent histone modifications, which collectively comprise the histone code, and which include such processes as acetylation, methylation, SUMOylation, glycosylation, ubiquitylation, and phosphorylation (3). The therapeutic relevance of these events is underscored by accumulating evidence indicating that agents capable of reversing these processes—e.g., DNMTIs or histone deacetylase inhibitors (HDACI)—are clearly capable of inducing re-expression of silenced genes in association with induction of transformed cell death. Moreover, representative agents of these classes have recently been approved for the treatment of hematologic malignancies, e.g., DNMTIs such as 5-azacytidine in the case of myelodysplastic syndrome (MDS), and HDACIs in the case of cutaneous T-cell lymphoma.

There is also evidence that these silencing mechanisms do not operate in a vacuum, but instead interact with each other, thereby providing a theoretical foundation for combinatorial approaches. For example, in preclinical studies, HDACIs have been shown to cooperate with DNMTIs to reverse gene silencing, and to block the proliferation and survival of transformed cells (4). Such findings have stimulated multiple clinical trials in which HDACIs are combined with hypomethylating agents, and preliminary results in certain diseases, e.g., leukemia, seem potentially promising (5). However, whether such outcomes actually reflect gene reactivation remains to be determined.

Although attempts to interfere with DNA methylation (e.g., by DNMTIs) and histone deacetylation (e.g., by HDACIs) have received the bulk of attention, recent efforts have begun to focus on pharmacologic disruption of other epigenetic regulatory processes. Histone methylation represents one such target. Histones can be methylated on arginine and lysine residues, and both the position and extent of methylation determine whether the mark stimulates or represses transcription (6). For example, methylation at H3K4, H3K36, and H3K79 is associated with enhanced transcription, whereas methylation at H3K9 and H3K27 is associated with transcriptional repression (7). Methyl residues (mono- and di-) are removed by a member of amine oxidase family (LSD1), whereas trimethylated residues are removed by Jumonji family proteins (ImjC; ref. 6). Clearly, interference with these events would be expected to alter histone methylation status and, as a consequence, modify gene transcription. However, the specific biologic effects of such interventions have not been extensively characterized.

This situation is now changing, at least in the case of histone methylation. Huang and colleagues describe the effects of a novel class of oligoamine analogs that function as potent inhibitors of LSD1, a FAD-dependent histone demethylase (6), in colon cancer cells (1). They report that these compounds substantially increased H3K4 mono- and di-methylation, events associated with enhanced transcription, and attenuated H3K9 dimethylation, a repressive mark. Notably, these events were associated with re-expression of aberrantly silent antagonists of the Wnt signaling pathway [i.e., secreted frizzled-related proteins (SFRP)]. Interestingly, co-exposure of cells to oligoamines in conjunction with a hypomethylating agent (5-azacytidine) resulted in pronounced inhibition of colon tumor cell growth both in vitro and in vivo. The authors conclude that modulation of histone methylation status, particularly when combined with disruption of DNA methylation, may represent a novel epigenetic form of therapy with significant therapeutic potential.

A novel oligoamine analog inhibitor of histone demethylases blocks colon tumor cell growth in association with histone methylation and gene re-expression. It also markedly potentiates the activity of hypomethylating agents in vitro and in vivo, suggesting that histone demethylase inhibitors may represent a valuable addition to the armamentarium of epigenetic agents. (Clin Cancer Res 2009;15[23]:7111–3)

Commentary on Huang et al., p. 7217

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Received 9/29/09; accepted 10/1/09; published OnlineFirst 11/24/09.

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© 2009 American Association for Cancer Research. doi:10.1158/1078-0432.CCR-09-2399

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This report provides the first evidence that histone demethylase inhibitors, as previously reported in the case of HDACIs (4), cooperate with DNMTIs to promote gene re-expression in transformed cells, a phenomenon accompanied by pronounced inhibition of cell growth and induction of cell death. They can also block the actions of co-repressor complexes. Oligoamine analog inhibitors of histone demethylases, i.e., LSD1, induce positive methylation marks on H3K4, accompanied by re-expression of Wnt pathway antagonist genes (SFRPs). Combined exposure of tumor cells with two agents that act at different levels of the epigenome (e.g., HDACIs and hypomethylating agents or hypomethylating agents and histone demethylase inhibitors) may be particularly effective in counteracting gene silencing and triggering transformed cell death. Abbreviations: 5-AC, 5-azacytidine; DAC, 5-aza-2¢-deoxycytidine; HDM, histone demethylase; HDHMI, histone demethylase inhibitor; HMT, histone methyltransferase; HMTI, histone methyltransferase inhibitor; LSD1, flavin-dependent amine oxidase histone demethylase; SWI/SNF complex, mating-type switching-sucrose nonfermenting complex.

Another question relates to the possibility that so-called epigenetic modulators may simultaneously act as cytotoxic agents. For example, both 5-aza-2¢-deoxycytidine and 5-azacytidine, currently viewed primarily as DNMTIs, were initially developed because of their direct cytotoxic activities (9). Although combination strategies incorporating epigenetic modulators generally employ sub- or minimally toxic concentrations of these agents when administered individually, it is conceivable that their limited cytotoxicity might be substantially increased by alterations in gene expression (e.g., down-regulation of DNA repair or anti-apoptotic genes). In fact, the possibility that perturbations in gene expression may cooperate with more direct cytotoxic actions to promote cell death seems quite likely. Whether histone demethylase inhibitors exert direct cytotoxic actions in addition to their effects on the epigenome remains to be determined.
attention to date, attention is currently beginning to focus on inhibitors of other proteins involved in epigenetic regulation, including, as described in the present study, histone demethylases, as well as histone methyltransferases and histone acetyltransferases, among numerous others. In addition, efforts to target other epigenetic components of the transcriptional control machinery e.g., co-repressor proteins, are well underway (10). Such considerations raise the possibility that in the future, combination chemotherapy regimens may consist of, instead of purely cytotoxic agents, multiple inhibitors (or activators) targeting distinct regulatory components of the epigenome (summarized in Fig. 1). In support of this notion, results of a recent study suggest that HDAC inhibitors enhance the lethal actions of histone methyltransferase inhibitors in human leukemia cells (11). Because our understanding of the epigenetic factors regulating gene expression, as well as our ability to target them, are advancing rapidly, the number of such regimens is potentially very large. Nevertheless, on the basis of, in part, the report by Huang and colleagues (1), such efforts seem well justified.

Disclosure of Potential Conflicts of Interest

No potential conflicts of interest were disclosed.

References

Targeting Histone Demethylases in Cancer Therapy

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Access the most recent version of this article at:
doi:10.1158/1078-0432.CCR-09-2399

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