Manipulating the Epigenome in Germinal Center Lymphomas: Is It Getting Easier and EZier?

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Mutations affecting key epigenetic modifiers tend to cluster in malignancies in which cells of origin lie in the germinal center (GC). EZH2, as transcriptional repressor, is mutated in high frequency in Chinese and Western patients with follicular lymphoma and may represent a rational target for GC-derived lymphomas. Clin Cancer Res; 20(12); 1–3. ©2014 AACR.
lymphocyte maturation and differentiation. This phenotype allows for an amplified proliferative state, in which additional mutations can accumulate further contributing to malignant transformation. Interestingly, these mutations are found almost exclusively in GC-derived lymphocytes, and these findings lend themselves toward building an epigenetic platform for the treatment of GC-derived malignancies.

In their article, Guo and colleagues further our understanding of the role of EZH2 in GC-derived malignancies. The authors demonstrate that EZH2 mutations are found in abundance in patients with FL and are associated with increased protein expression. The frequencies of these mutations and increased expression were similar to those reported previously and confirm that this is a global finding, demonstrating that patients from divergent ethnic backgrounds have similar patterns of expression and mutation frequencies (16.9%) compared with grade 3 FL. They also demonstrate a significant association with grade 3 FL patients (26.8%). The authors further define EZH2 mutations as being more prevalent in grades 1 and 2 as compared with grade 3 FL. They also demonstrate a significant association with BCL2 rearrangements in both Chinese and Western cohorts.

The notion of epigenetic targeting of GC lymphomas began with observations that the effects of both p53 and Bcl6 could be modified by acetylation. There is a critical inverse relationship between Bcl6 and p53, the functional status of which is linked to each transcription factor’s degree of acetylation. Deacetylation of Bcl6 is required for the transcriptional repressor effects of this oncogene. Conversely, acetylation activates the tumor suppressor, p53. One potential therapeutic strategy for targeting GC lymphomas involves the pharmacologic modification of Bcl6 and p53 using histone deacetylase (HDAC) inhibitors. Bcl6 and p53 are known to be acetylated in lymphoma cell lines treated with HDAC inhibitors in combination with the sirtuin inhibitor, nicinamide. This correlates with synergistic cytotoxicity that is restricted to GC lymphomas (10). This finding has been translated to the clinical setting for evaluation of vorinostat in combination with nicinamide for relapsed and refractory lymphomas. In a heavily pretreated cohort of patients, the combination led to a 24% overall response rate and an additional 57% of patients who achieved stable disease. This proof-of-principle study used two first-in-class drugs, which can be greatly improved upon, and despite this demonstrated that Bcl6 and p53 can be therapeutically modulated (10). Hypomethylating agents have also been studied in this context, both alone and in combination with HDAC inhibitors or combination chemotherapy. The HDAC inhibitor panobinostat is synergistic with the hypomethylating agent decitabine in preclinical models of DLBCL. The combination led to increased acetylation of histone 3 with unique effects on gene expression and gene-specific CpG methylation. The effects of this combination correlated with synergistic cytotoxicity in cell lines and tumor growth delay in in vivo models of DLBCL (11). Similar to these findings, preexposure with decitabine prior to chemotherapy led to enhanced chemosensitivity in cell lines refractory to doxorubicin and induction of hypomethylation, decreased growth rate, and reactivation of SMAD1, which plays a role in differentiation, proliferation, and apoptosis, as well as chemotherapy-induced senescence. Following a 5-day exposure to decitabine in lymphoma cell lines, SMAD1 expression was increased 5-fold. This finding was translated clinically in patients with de novo DLBCL who received a preexposure of
decitabine followed by R-CHOP. The preexposure led to decreased methylation marks in paired tissue samples and was well tolerated in this early-phase study (12).

These epigenetic strategies could potentially lead to a therapeutic effect by modulating the constitutively active EZH2–PC2 complex in GC malignancies. In addition, new EZH2 inhibitors are presently in development by GlaxoSmithKline and Epizyme, which have demonstrated activity in GC lymphomas (13). These agents have shown potent activity in preclinical models in which EZH2 is either mutated or wild-type EZH2 is overexpressed, and they are now being studied in early-phase clinical trials. These findings support the potential benefit of EZH2 inhibitors for the treatment of GC lymphomas. EZH2 inhibitors may be potently synergistic with other epigenetic modifying agents such as HDAC inhibitors and hypomethylating agents—an area yet to be studied. Hopefully, similar to the remarkable activity in GC lymphomas (13). These agents have shown potent activity in preclinical models in which EZH2 is either mutated or wild-type EZH2 is overexpressed, and they are now being studied in early-phase clinical trials. These findings support the potential benefit of EZH2 inhibitors for the treatment of GC lymphomas. EZH2 inhibitors may be potently synergistic with other epigenetic modifying agents such as HDAC inhibitors and hypomethylating agents—an area yet to be studied. Hopefully, similar to the remarkable

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