EZH2 plays a critical role in B-cell maturation and in non-Hodgkin’s lymphoma: Interplay between EZH2 function and B-cell activation

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Abstract

The EZH2 inhibitor tazemetostat (EPZ-6438) is emerging as a promising therapeutic agent for the treatment of non-Hodgkin's lymphoma (NHL). A significant body of work has now demonstrated in vitro and in vivo effects of EZH2 inhibition in preclinical models of lymphoma, in addition to objective clinical responses in early human trials. While EZH2 gain-of-function mutations clearly contribute to lymphomagenesis, patients with lymphomas harboring wild-type EZH2 also show responses to tazemetostat. This suggests a broad role of EZH2 in B-cell oncogenesis. Several recent mouse model studies have demonstrated the importance of wild-type EZH2 catalytic activity in the formation of germinal centers in non-diseased lymph nodes, suggesting a central role for EZH2 in B-lymphocyte maturation. These findings indicate that the importance of EZH2 to B-cell lymphoma likely lies in its ability to regulate B-cell differentiation. To understand the relationship between B-cell maturation and sensitivity to EZH2 inhibition, we evaluated changes in maturation markers and cellular proliferation following treatment of diffuse large B-cell lymphoma (DLBCL) cell lines with tazemetostat in combination with modulators of B-cell activation. Consistent with the importance of EZH2 in the regulation of B-cell differentiation, we observed increased expression of B-cell maturation markers in DLBCL cell lines treated with single agent tazemetostat in vitro. Furthermore, we demonstrate that tazemetostat pre-treatment of subsets of DLBCL cell lines (both EZH2 mutant and wild-type) can sensitize cells to inhibitors of B-cell activation pathways, which include glucocorticoids and BTK, MALT1 and PI3K pathway inhibitors. While the anti-proliferative activity of single agent tazemetostat can be diminished or delayed by co-treatment with biological stimulators of B-cell activation including B-cell receptor ligation, CD40L, LPS and BAFF. Importantly, B-cell receptor ligation and co-stimulation agents have little proliferative effects on DLBCL cell lines on their own, suggesting that the protective function of these agents is directly related to the effects of EZH2 inhibition and not a generic stimulator of proliferation. Our findings suggest that EZH2 inhibition initiates a differentiation program that enables lymphoma cells to proceed through the normal processes of B-cell selection, growth regulation and maturation.

Background

1) EZH2 inhibitors are emerging as valuable therapeutic agents for the treatment of non-Hodgkin’s lymphoma.
2) The mechanism by which EZH2 inhibitors inhibit lymphoma cell proliferation is still poorly understood.
3) EZH2 is known to be a regulator of B-cell maturation and germinal center formation.¹,²
4) Lymphomas with gain of function mutations in EZH2 predominantly have a germinal center phenotype.³,⁴
5) EZH2 inhibition induces differentiation markers in lymphoma cells.
6) Does EZH2's role in B-cell maturation contribute to the anti-lymphoma activity of tazemetostat?

Does Tazemetostat (EPZ-6438) poise lymphoma cells for terminal differentiation?

Results

1) EZH2 inhibitors are emerging as valuable therapeutic agents for the treatment of non-Hodgkin’s lymphoma.
2) The mechanism by which EZH2 inhibitors inhibit lymphoma cell proliferation is still poorly understood.
3) EZH2 is known to be a regulator of B-cell maturation and germinal center formation.¹,²
4) Lymphomas with gain of function mutations in EZH2 predominantly have a germinal center phenotype.³,⁴
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6) Does EZH2's role in B-cell maturation contribute to the anti-lymphoma activity of tazemetostat?

Conclusions

• EZH2 regulates maturation of both normal B-cells and lymphoma cells.
• B-cell differentiation effects are observed in both WT and Mutant EZH2 NHL cell lines in response to tazemetostat.
• EZH2 inhibition creates a dependency on B-cell activation signals.
• Tazemetostat treatment may allow lymphoma cells to attempt to proceed through the normal processes of B-cell maturation and selection.