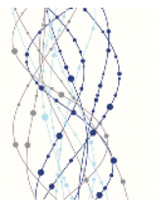
Melanoma

Major finding: Histone variant H2A.Z.2 promotes melanoma cell proliferation via induction of E2F target genes.

Mechanism: H2A.Z.2 promotes BRD2 and E2F1 recruitment to E2F target genes that regulate cell-cycle progression.

Impact: Disruption of the H2A.Z.2–BRD2–E2F1 axis may improve drug sensitivity in malignant melanoma.

THE HISTONE VARIANT H2A.Z.2 REGULATES PROLIFERATION IN MELANOMA



Histone variants have been implicated as key epigenetic regulators in melanoma and other cancers. H2A.Z.1 and H2A.Z.2 are distinct isoforms of the histone H2A variant H2A.Z, which has an established role in regulating transcription and is overexpressed in several tumor types. Vardabasso and colleagues found that H2A.Z.1 and H2A.Z.2 were expressed at higher levels in melanoma compared with benign nevi, and that higher expression correlated with lower survival in patients with metastatic melanoma. Knockdown of H2A.Z.2, but not H2A.Z.1, induced G1/S cell-cycle arrest in melanoma cells. Transcriptional profiling revealed that H2A.Z.2 positively regulates the expression of E2F target genes involved in cell-cycle progression; H2A.Z.2 binding was increased at the promoter but depleted in the gene body of H2A.Z.2-regulated genes in melanoma cells. In addition, bromodomain-containing 2 (BRD2), a member of the BET family of proteins that couples histone acetylation to transcription, was enriched in H2A.Z.1- and H2A.Z.2-containing nucleosomes, and colocalized with H2A.Z and E2F1 at E2F target genes in melanoma cells. Furthermore, high levels of BRD2 were detected in metastatic melanoma cell lines and in primary and metastatic melanoma specimens from human patients. Similar to the effects of H2A.Z.2 depletion, knockdown of BRD2 induced G1/S cell-cycle arrest and reduced the expression of E2F target genes, suggesting that H2A.Z.2 and BRD2 cooperate to promote E2F target gene transcription. Consistent with this idea, knockdown of H2A.Z.2 decreased histone acetylation and impaired BRD2 and E2F1 recruitment to target gene promoters. Intriguingly, H2A.Z.2 depletion also enhanced the sensitivity of melanoma cells to BET inhibitors, chemotherapy, and MEK inhibition. Taken together, these findings suggest that H2A.Z.2 promotes and maintains BRD2, E2F1, and histone acetylation levels to drive melanoma proliferation and suggest a potential epigenetic therapeutic strategy to improve drug sensitivity in malignant melanoma. ■

Vardabasso C, Gaspar-Maia A, Hasson D, Pünzeler S, Valle-Garcia D, Straub T, et al. Histone variant H2A.Z.2 mediates proliferation and drug sensitivity of malignant melanoma. Mol Cell 2015;59: 75–88.

Clinical Trials

Major finding: Belinostat induces durable responses and is well tolerated in patients with relapsed or refractory PTCL.

Concept: T-cell lymphomas exhibit epigenetic defects and are sensitive to pan-HDAC inhibitors.

Impact: The combination of belinostat with other therapeutic regimens may improve outcome in PTCL.

BELINOSTAT IS ACTIVE IN PERIPHERAL T-CELL LYMPHOMA

Current treatments for peripheral T-cell lymphoma (PTCL), a group of aggressive non-Hodgkin lymphomas associated with poor prognosis, fail to induce clinical responses in many cases, and patients frequently experience tumor relapse. Previous studies have indicated that T-cell lymphomas are often characterized by mutations in epigenetic regulators and exhibit sensitivity to histone deacetylase (HDAC) inhibitors, prompting O'Connor and colleagues to evaluate the efficacy and safety of the pan-HDAC inhibitor belinostat in PTCL in a phase II clinical trial. The response to single-agent treatment with belinostat was assessed in 120 patients with relapsed or refractory PTCL, many of whom had received multiple prior systemic therapies. Belinostat treatment resulted in an overall response rate of 25.8% (31 of 120 patients) and induced complete responses in 13 (10.8%) patients and partial responses in 18 (15%) patients; median progression-free survival was 1.6 months and median overall survival was 7.9 months. In addition, 63.3% of patients exhibited decreased tumor volume, and belinostat treatment enabled 12 patients to undergo hematopoietic stem cell transplant. These responses were observed across PTCL subtypes and were durable, with a median duration of response of 13.6 months and an ongoing response greater than 36 months in one patient. Belinostat monotherapy was well tolerated and generally resulted in mild to moderate adverse events that did not require dose reductions; the most common grade 3–4 treatment-related toxicities were anemia, thrombocytopenia, dyspnea, and neutropenia. These findings demonstrating the antitumor activity of belinostat resulted in its recent approval by the FDA for patients with relapsed or refractory PTCL and suggest that the combination of belinostat with other therapeutic agents may improve clinical outcomes in PTCL. ■

O'Connor OA, Horwitz S, Masszi T, Van Hoof A, Brown P, Doorduijn J, et al. Belinostat in patients with relapsed or refractory peripheral T-cell lymphoma: results of the pivotal phase II BELIEF (CLN-19) study. J Clin Oncol 2015 Jun 22 [Epub ahead of print].

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