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Lymphoma

Major finding: BCL6 recruits LSD1 to enhancers to silence genes and promote germinal center–derived lymphomagenesis.

Concept: Blocking LSD1 enzymatic activity is insufficient to suppress BCL6-driven lymphoma cell proliferation.

Impact: Destabilization of LSD1 interactions may be a potential therapeutic strategy for BCL6-dependent lymphomas.

BCL6-DRIVEN LYMPHOMA IS DEPENDENT ON LSD1 COREPRESSION

Chromatin regulatory proteins play a central role in orchestrating the function of germinal centers (GC), where mature B cells must transiently repress genes involved in immune signaling, cell-cycle checkpoints, and DNA damage responses to undergo rapid proliferation and somatic hypermutation and allow for successful immunoglobulin affinity maturation. The transition through this hyperproliferative and genetically unstable state must be tightly regulated, and deregulation of this process can lead to malignant B-cell transformation. Based on prior observations showing loss of histone methylation at enhancers for genes repressed in GC B cells, Hatzi and colleagues investigated the role of histone demethylases in regulating GC formation and function. Among histone demethylases, LSD1 was most consistently upregulated in GCs, and conditional deletion of *Lsd1* in GC B cells significantly impaired the formation of GCs and their ability to generate high-affinity antibodies. *Lsd1*-deficient B cells exhibited increased enhancer chromatin accessibility and increased expression of genes normally silenced in GC B cells that are also targets of the transcriptional repressor BCL6, a key regulator of GC function that is frequently translocated and constitutively expressed in B-cell lymphoma. BCL6 physically interacted with LSD1 and recruited LSD1 to its target genes, indicating that LSD1 acts in concert with BCL6 to facilitate proliferation and dampen immune signaling during humoral immune responses. *Lsd1* deletion in mice with constitutive *Bcl6* expression also rescued BCL6-driven GC hyperplasia, delayed lymphomagenesis, and prolonged survival, demonstrating that LSD1 is also required for BCL6-driven GC B-cell transformation. These findings raise the possibility that LSD1 could be a therapeutic target in BCL6-dependent lymphomas; however, catalytic inhibition of LSD1 did not have the same effect on GC formation as total LSD1 loss, and an LSD1 domain required for protein–protein interactions was instead required for lymphoma cell proliferation, raising the possibility that inhibitors that destabilize LSD1 may have activity in BCL6-driven lymphomas. ■

Hatzi K, Geng H, Doane AS, Meydan C, LaRiviere R, Cardenas M, et al. Histone demethylase LSD1 is required for germinal center formation and BCL6-driven lymphomagenesis. Nat Immunol 2019;20:86–96.

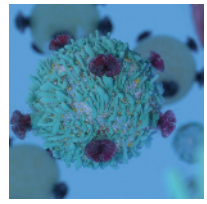
Immunotherapy

Major finding: Regulation of PD-1 protein degradation by FBXO38 is necessary for T-cell antitumor activity.

Mechanism: FBXO38 induces Lys48-linked polyubiquitination and proteasomal degradation of internalized PD-1.

Impact: *FBXO38* expression is downregulated in tumor-infiltrating T cells and can be restored by IL2 therapy.

THE E3 LIGASE FBXO38 CONTROLS PD-1 EXPRESSION AND ANTITUMOR IMMUNITY



Aberrant upregulation of the immune checkpoint protein PD-1 on intratumoral T cells results in impaired antitumor immunity, emphasizing the importance of understanding the mechanisms that control PD-1 expression. Transcriptional regulation of the gene encoding PD-1 has been well characterized, but whether PD-1 protein levels are also regulated has not been determined. Meng, Liu, and colleagues found that PD-1 protein was ubiquitinated following internalization from the cell surface and was subsequently degraded by the proteasome in activated human T cells. The F-box protein FBXO38, a member of the SKP1–CUL1–F-box protein family of E3 ubiquitin ligases, interacted with PD-1 and decreased PD-1 cell-surface expression on activated T cells. Consistent with a role in mediating PD-1 downregulation, FBXO38 directly induced Lys48-linked polyubiquitination of internalized PD-1 at Lys233, leading to PD-1 proteasomal degradation. Mice with conditional deletion of *Fbxo38* in T cells did not exhibit changes in T-cell receptor or CD28 signaling, but displayed higher cell-surface levels of PD-1 on tumor-infiltrating T cells and enhanced tumor progression compared to wild-type mice. This increase in tumor growth was reversed by anti–PD-1 therapy, implicating PD-1 as the main target of FBXO38. *FBXO38* transcription was downregulated in both human and mouse tumor-infiltrating $CD8^+PD\text{-}1^+$ T cells, but could be restored by treatment with IL2, which stimulated *FBXO38* transcription via the downstream transcription factor STAT5. Moreover, IL2 administration decreased PD-1 expression on the surface of tumor-infiltrating T cells and showed better antitumor effects in wild-type mice than mice with T cell–specific deletion of *Fbxo38*. These results define FBXO38 as a critical mediator of PD-1 protein degradation that is required for maintenance of antitumor immunity and suggest targeting IL2-mediated regulation of *FBXO38* expression as a potential strategy to block PD-1 signaling in tumors. ■

Meng X, Liu X, Guo X, Jiang S, Chen T, Hu Z, et al. FBXO38 mediates PD-1 ubiquitination and regulates anti-tumour immunity of T cells. Nature 2018;564:130–5.

AACR American Association for Cancer Research

CANCER DISCOVERY

The E3 Ligase FBXO38 Controls PD-1 Expression and Antitumor Immunity

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