Hematologic Cancers

Major finding: Blastic plasmacytoid dendritic cell neoplasms (BPDCN) depend on a TCF4/BRD4 transcriptional program.

Approach: An RNAi screen and high-throughput small-molecule screen identify BRD4 as a druggable target in BPDCN.

Impact: BET inhibitors warrant further investigation for the treatment of patients with BPDCN.

BET INHIBITORS TARGET BLASTIC PLASMACYTOID DENDRITIC CELL NEOPLASMS

Blastic plasmacytoid dendritic cell neoplasm (BPDCN) is an aggressive hematologic malignancy that arises from plasmacytoid dendritic cells (pDC), innate immune cells whose lineage commitment is controlled by the E-box transcription factor TCF4. BPDCN has a poor survival rate and most patients develop drug-resistant disease. Thus, a better understanding of the molecular pathways underlying BPDCN may lead to new targeted therapies. Ceribelli and colleagues performed a loss-of-function RNAi screen and identified TCF4 as an essential regulator required for BPDCN cell survival. Chromatin immunoprecipitation sequencing combined with gene expression profiling in BPDCN cells revealed 399 genes upregulated by TCF4 and 630 genes downregulated by TCF4, most of which were bound by TCF4 at E-box motifs in the promoter or gene body. Genes upregulated by TCF4 included genes required for pDC development and function, and oncogenes including *MYC*, *BCL2*, *TCL1A*, and *TCL1B*. The pDC genes were more highly expressed in normal pDCs compared with BPDCNs, whereas the oncogenes were more highly expressed in BPDCNs. Strong homogenous expression of TCF4 was observed in 24 out of 28 BPDCN tumors, suggesting the possibility of using TCF4 expression as a diagnostic marker of BPDCN. A high-throughput drug screen testing 1,910 small molecules found that BPDCN cells were specifically sensitive to three different bromodomain and extra-terminal domain (BET) inhibitors, and BET inhibition reduced the growth of BPDCN xenografts. The BET protein BRD4 was also a top hit in the siRNA screen, indicating it may be the target of BET inhibition. Moreover, BET inhibition targeted the TCF4 transcriptional network, reducing expression of TCF4 and its target genes and decreasing TCF4 occupancy of target genes. Further, BRD4 occupancy defined BPDCN superenhancers, one of which regulated TCF4 expression and was bound by TCF4 itself. Together, these data indicate that a TCF4/BRD4 transcriptional network underlies BPDCN and suggest that BET inhibitors may potentially be effective in patients with BPDCN. ■

Ceribelli M, Hou ZE, Kelly PN, Huang DW, Wright G, Ganapathi K, et al. A druggable TCF4- and BRD4-dependent transcriptional network sustains malignancy in blastic plasmacytoid dendritic cell neoplasm. Cancer Cell 2016;30:764–78.

Immune Evasion

Major finding: Inflammatory TNFα signaling stabilizes PD-L1 to promote tumor immune evasion and tumor growth.

Mechanism: TNFα/NF-κB signaling upregulates CSN5 to deubiquitinate and stabilize PD-L1 and promote immune escape.

Impact: Inhibition of CSN5 may enhance the efficacy of cancer immunotherapies including anti-CTLA4.

CHRONIC INFLAMMATION PROMOTES CSN5-MEDIATED PD-L1 STABILIZATION

Cancer cells can evade immune surveillance in part through expression of the inhibitory programmed cell death-ligand 1 (PD-L1) on their cell surface. Although transcriptional mechanisms of PD-L1 regulation have been described, the mechanisms by which PD-L1 is post-translationally regulated have not been well elucidated. Lim, Li, and colleagues investigated antitumor immunity in a mouse model of inflammation, finding that inflammation enhanced tumor growth and increased the number of tumor-infiltrating lymphocytes and macrophages, but reduced the cytotoxic activity of T cells, indicating that inflammation prevents T-cell antitumor activity. In breast cancer cells, inflammatory cytokines released by macrophages induced upregulation of PD-L1 protein, but not mRNA, indicative of post-translational regulation. Mechanistically, inflammation induced macrophages to secrete TNFα that activated tumor cell NF-κB signaling, allowing the p65 subunit to bind to the promoter and enhance transcription of COP9 signalosome 5 (*CSN5*; also known as *COPS5*). *CSN5* encodes a deubiquitinating enzyme that was found to deubiquitinate and stabilize PD-L1, resulting in enhanced PD-L1 expression in response to inflammatory TNFα signaling. Further, the CSN5 inhibitor curcumin blocked TNFα-induced PD-L1 stabilization in multiple cancer cell types. In breast cancer cell lines and in tissue from patients with breast cancer, CSN5 expression was correlated with expression of PD-L1, providing support for the *in vitro* findings. Moreover, elevated CSN5 expression was associated with shorter survival in patients with breast cancer. Anti-PD1 antibodies have been combined with anti-CTLA4 antibodies in clinical trials, providing a rationale for testing curcumin in combination with CTLA4 blockade. Curcumin enhanced the therapeutic efficacy of anti-CTLA4 in mice, resulting in reduced tumor burden, increased survival, and an increase in active tumor-infiltrating $CD8^+$ T cells. In addition, curcumin plus anti-CTLA4 was effective in reducing tumor growth in noninflammatory conditions. Collectively, these findings indicate that CSN5 stabilizes PD-L1 to promote tumor immune evasion and that inhibition of CSN5 may be effective in combination with other immunotherapies. ■

Lim SO, Li CW, Xia W, Cha JH, Chan LC, Wu Y, et al. Deubiquitination and stabilization of PD-L1 by CSN5. Cancer Cell 2016;30:925–39.