Epigenetics

Major finding: Mutations in the MLL3 PHD domain promote oncogenesis by disrupting its interaction with BAP1.

Concept: BAP1 recruits MLL3 to chromatin, facilitating H3K4 monomethylation and expression of tumor suppressors.

Impact: EZH2 may be a potential therapeutic target in patients with mutations in *MLL3* or other COMPASS subunits.

MLL3 MUTATIONS DISRUPT COMPASS RECRUITMENT TO ENHANCER CHROMATIN

MLL3 is a lysine methyltransferase subunit of the COMPASS complex responsible for monomethylation of histone H3 lysine 4 (H3K4). *MLL3* is frequently mutated in a variety of tumor types, but the mechanism by which these mutations promote tumorigenesis remains unclear, prompting Wang and colleagues to investigate the role of *MLL3* mutations in cancer. Analysis of data from The Cancer Genome Atlas revealed two *MLL3* mutational hotspots within the N-terminal PHD finger repeats that are associated with cancer. Mass spectrometry showed that this N-terminal region of MLL3 interacted with the histone deubiquitinating BAP1 complex, whereas other COMPASS family proteins did not interact with BAP1. In patients with breast cancer, *MLL3* mutations in the PHD repeats were associated with reduced disease-free survival, and, in breast cancer cells, these mutations reduced the interaction between MLL3 and BAP1. Further, *MLL3* PHD domain mutations were identified in lung adenocarcinoma, bladder carcinoma, breast cancer, and colon adenocarcinoma. Mechanistically, BAP1 recruited MLL3 to enhancer chromatin to promote H3K4 monomethylation. Thus, deletion of *BAP1* or mutation of the *MLL3* PHD domain reduced MLL3 activity at enhancers. MLL3 depletion decreased expression of tumor suppressor genes from BAP1-dependent enhancers and accelerated the growth of breast cancer xenografts. *MLL3* mutations or BAP1 deficiency also reduced recruitment of the H3K27 demethylase KDM6A, a component of MLL3-COMPASS, to enhancers, thereby increasing H3K27 trimethylation. Consistent with these findings, using an EZH2 inhibitor to block the H3K27 methyltransferase activity of PRC2 restored normal gene expression patterns in MLL3-mutant cells, and reduced tumor growth and extended survival *in vivo*. In addition to elucidating a mechanism by which *MLL3* mutations may contribute to oncogenesis, these findings suggest the potential for therapeutic targeting of EZH2 in tumors with COMPASS subunit mutations. ■

Wang L, Zhao Z, Ozark PA, Fantini D, Marshall SA, Rendleman EJ, et al. Resetting the epigenetic balance of Polycomb and COMPASS function at enhancers for cancer therapy. Nat Med 2018;24:758–69.

Pancreatic Cancer

Major finding: Unresolved ER stress promotes quiescence and immune escape of latent disseminated PDAC.

Approach: Metastatic mouse PDAC cells that can be selectively ablated were used to generate a model of latent PDAC.

Impact: Reversal of ER stress in DCCs may be a therapeutic strategy to reduce latent pancreatic metastases.

ENDOPLASMIC RETICULUM STRESS DRIVES LATENT PANCREATIC TUMOR METASTASES

Patients with pancreatic ductal adenocarcinoma (PDAC) often relapse after surgical resection of the primary tumor due to metastatic colonization, which occurs prior to diagnosis. Immunity has been shown to prevent the outgrowth of quiescent disseminated cancer cells (DCC), which give rise to microscopic latent metastases. Having identified the presence of hepatic DCCs in livers from patients with PDAC and an autochthonous mouse model of PDAC, Pommier and colleagues generated a fluorescently labeled metastatic mouse PDAC cell line (mM1DTLB) that recapitulates human PDAC harboring hepatic DCCs and can be selectively ablated by treatment with diphtheria toxin (DT) to elucidate the mechanisms underlying disseminated tumor cell latency in PDAC. Intrasplenic injection of mM1DTLB into mice after the DT-mediated ablation of subcutaneous mM1DTLB tumors ("preimmunization") resulted in the presence of single MHCI$^-$/CK19$^-$/ECAD$^-$ DCCs and decreased macrometastases compared with mice that received only an intrasplenic injection of mM1DTLB. Depletion of CD4$^+$ and CD8$^+$ T cells in preimmunized mice after the appearance of DCCs resulted in the outgrowth of latent DCCs and MHCI$^+$/CK19$^+$ macrometastases. Small MHCI$^-$/ECAD$^-$ and CK19$^-$ subpopulations of mM1DTLB cells grown *in vitro* phenotypically resembled DCCs *in vivo*, and injection of ECAD$^+$, but not ECAD$^-$, mM1DTLB cells resulted in the formation of macrometastases, suggesting that MHCI$^-$/ECAD$^-$/CK19$^-$ mM1DTLB cells are precursors of quiescent DCCs. Further, ECAD$^-$ cells exhibited increased expression of genes related to the endoplasmic reticulum (ER) stress response, particularly the transcription factor CHOP, which was expressed by hepatic DCCs in preimmunized mice as well as mice and patients with PDAC; however, ECAD$^+$ cells, human PDAC, and hepatic murine macrometastases exhibited increased activation of the IRE1a/XBP1 pathway, which is required to resolve ER stress, compared with ECAD$^-$ cells and murine and human hepatic DCCs. These results describe the cell-autonomous mechanism by which disseminated PDAC cells enter quiescence and evade immune surveillance while maintaining the potential for PDAC outgrowth. ■

Pommier A, Anaparthy N, Memos N, Kelley ZL, Gouronnec A, Yan R, et al. Unresolved endoplasmic reticulum stress engenders immune-resistant, latent pancreatic cancer metastases. Science 2018 May 17 [Epub ahead of print].