Drug Design

Major finding: The GSK3α-selective inhibitor BRD0705 promotes AML cell differentiation without increasing β-catenin.

Approach: Targeting the Asp-Glu switch in the kinase hinge allows design of selective GSK3α and GSK3β inhibitors.

Impact: Selective GSK3α inhibition may be feasible and beneficial for the treatment of patients with AML.

A PARALOG-SELECTIVE INHIBITOR MAY ALLOW FOR TARGETING OF GSK3α IN AML

Glycogen synthase kinase 3α (GSK3α) has emerged as a potential therapeutic target in acute myeloid leukemia (AML), as its genetic suppression promotes AML cell differentiation and reduces leukemic progression. However, selective GSK3α inhibitors are lacking. The ATP-binding site of GSK3α is highly similar to its paralog GSK3β, sharing 95% identity. Thus, previous ATP-competitive inhibitors target both GSK3α and GSK3β, and these dual inhibitors stabilize β-catenin, promote myeloid cell transformation, and exhibit mechanism-based toxicities. Wagner, Benajiba, and colleagues sought to develop paralog-specific GSK3 inhibitors targeting the Asp-Glu "switch" in the kinase hinge, the single amino acid difference in the ATP-binding domain with a Glu in GSK3α and an Asp in GSK3β. Structure-based design yielded the GSK3α-selective inhibitor BRD0705 and the GSK3β-selective inhibitor BRD3731. GSK3α inhibition with BRD0705 did not stabilize β-catenin in AML cells, whereas BRD3731 did in a subset of AML cell lines. GSK3α inhibition with BRD0705 effectively suppressed GSK3α kinase activity, induced differentiation, and impaired colony formation in AML cell lines and primary cells. In contrast, the effects of BRD3731 were inconsistent, indicating that GSK3α-selective inhibition may be beneficial in AML. RNA sequencing revealed that BRD0705 induced expression of differentiation transcriptional programs and downregulated stemness gene signatures without increasing the β-catenin transcriptional signature. Conversely, the dual inhibitor BRD0320 strongly induced β-catenin signaling pathway genes, further demonstrating that inhibition of GSK3α and GSK3β have different effects. *In vivo*, BRD0705 suppressed AML growth and extended survival in xenografts and syngeneic mouse models with no apparent toxicity to normal hematopoietic cells. In addition to providing insight into the paralog-specific functions of GSK3α and GSK3β, these findings suggest that GSK3α inhibition may be a feasible therapeutic approach in patients with AML. ■

Wagner FF, Benajiba L, Campbell AJ, Weïwer M, Sacher JR, Gale JP, et al. Exploiting an Asp-Glu "switch" in glycogen synthase kinase 3 to design paralog-selective inhibitors for use in acute myeloid leukemia. Sci Transl Med 2018;10:eaam8460.

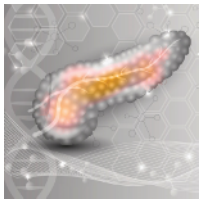
Pancreatic Cancer

Major finding: Loss of the X chromosome–encoded KDM6A aberrantly activates oncogenic superenhancers.

Concept: KDM6A loss in females or KDM6A/UTY loss in males induces metastatic squamous-like pancreatic cancer.

Impact: KDM6A-mutant pancreatic cancers may be sensitive to treatment with BET inhibitors.

KDM6A LOSS INDUCES AGGRESSIVE PANCREATIC CANCER IN MICE



KDM6A is an X chromosome–encoded histone demethylase and a component of the COMPASS-like complex, which monomethylates H3K4 to delimit enhancer chromatin. It is frequently mutated in a variety of tumor types including pancreatic cancer and its loss of function has been linked to tumorigenesis. However, the mechanisms by which KDM6A loss promotes pancreatic cancer remain poorly understood. Andricovich and colleagues found that mutations and deletions in *KDM6A* occurred frequently in squamous-like and metastatic pancreatic cancer. In mice with $Kras^{G12D}$-driven PanIN lesions, which rarely progress to invasive pancreatic cancer, loss of *Kdm6a* induced aggressive, metastatic squamous-like pancreatic tumors in female mice, whereas male mice developed well differentiated pancreatic ductal adenocarcinoma. In male mice, concomitant loss of the Y chromosome-encoded KDM6 family member *UTY*, which lacks demethylase activity, resulted in a similar phenotype to *Kdm6a* loss alone in female mice. *Kdm6a* loss resulted in gene expression changes independent of H3K27me3 that promoted squamous and quasi-mesenchymal differentiation in female mice. Mechanistically, loss of KDM6A deregulated the COMPASS-like complex, disrupting the superenhancer landscape to promote aberrant activation oncogenes including *ΔNp63*, *MYC*, and *RUNX3*, suggesting the potential for epigenetic inhibitor therapies. A small-molecule screen in 17 human pancreatic cancer cell lines revealed that *KDM6A*-deficient cells are sensitive to bromodomain and extraterminal domain (BET) inhibitors including JQ1, iBET151, and bromosporine. JQ1 treatment reduced BRD4 occupancy at the superenhancers driving *ΔNp63*, *MYC*, and *RUNX3* expression. *In vivo*, JQ1 treatment inhibited squamous differentiation and suppressed the growth of *Kdm6a*-deficient pancreatic tumors. The identification of KDM6A loss as a gender-specific driver of oncogenic superenhancer activation in pancreatic cancer suggests the potential for BET inhibitors for the treatment of patients with KDM6A-deficient tumors. ■

Andricovich J, Perkail S, Kai Y, Casasanta N, Peng W, Tzatsos A. Loss of KDM6A activates super-enhancers to induce gender-specific squamous-like pancreatic cancer and confers sensitivity to BET inhibitors. Cancer Cell 2018;33:512–26.e8.