Published OnlineFirst December 6, 2019; DOI: 10.1158/2159-8290.CD-RW2019-183

Drug Discovery

Major Finding: SD-36, a small-molecule proteolysis-targeting chimera (PROTAC), causes STAT3 degradation *in vivo*.

Concept: SD-36 treatment caused complete and lasting tumor regression in mouse leukemia and lymphoma models.

Impact: Further studies of SD-36 and continued development of other anticancer PROTACs may be fruitful.

A SMALL-MOLECULE DRUG TARGETING STAT3 CAUSES TUMOR REGRESSION IN MICE

Attempts have been made to develop anticancer drugs targeting the transcription factor signal transducer and activator of transcription 3 (STAT3), but none have yet been successful. Bai, Zhou, Xu, Zhao, and colleagues used structure-based design to develop a small-molecule proteolysis-targeting chimera (PROTAC) that specifically flags STAT3 for degradation. The PROTAC, named SD-36, is capable of permeating the cell membrane and binds STAT3 with high affinity. Experiments in human acute myeloid leukemia (AML) and anaplastic large-cell lymphoma cell lines showed that SD-36 is a bona fide PROTAC STAT3 degrader that directly interacts with STAT3's SH2 domain in cells. Proteomic analyses revealed that SD-36 exhibits high selectivity for STAT3 in cells—of approximately 5,500 proteins quantified, including other STAT family members, only STAT3 had its levels reduced by 2-fold or more upon SD-36 treatment. Demonstrating the functional relevance of these findings, SD-36 treatment caused dysregulation of known STAT3-target genes in cells. SD-36 exerted growth-inhibitory effects attributed to G_1 arrest and increases in apoptosis in one of nine tested AML cell lines and five of nine tested lymphoma cell lines; in at least one cell line, this effect appeared dependent on downregulation of c-MYC. Mouse experiments revealed that SD-36 treatment resulted in selective and enduring degradation of STAT3 in xenografted tumors, hinting at the PROTAC's therapeutic potential. In three mouse xenograft models of leukemia and lymphoma, SD-36 treatment caused complete and durable tumor regression without causing weight loss or signs of overt toxicity. Tests in immunocompetent mice showed that SD-36 treatment was well tolerated and led to marked decreases in STAT3 levels in four representative tissues (liver, spleen, kidney, and heart). These findings not only suggest that continued development of SD-36 may be a promising avenue of research but also show that a PROTAC-based strategy for targeting the supposedly "undruggable" STAT3 is feasible. ■

Bai L, Zhou H, Xu R, Zhao Y, Chinnaswamy K, McEachern D, et al. A potent and selective small-molecule degrader of STAT3 achieves complete tumor regression in vivo. Cancer Cell 2019;36:498–511.e17.

Mutations

Major Finding: Genomic analysis identified previously unknown potential histiocytosis-driving mutations.

Concept: In a set of twins with histiocytosis, a *CSF1R*-mutant yolk-sac precursor was the disease originator.

Impact: Patients with histiocytoses treated according to the newly defined mutations exhibited responses.

MUTATIONS IN RECEPTOR TYROSINE KINASES DRIVE HISTIOCYTIC DISORDERS

The development of histiocytoses, clonal hematopoietic disorders of unclear cellular origin, is poorly understood, and therapeutic targets have generally been limited to BRAF and MEK, two kinases thought to drive many of these disorders. In a genomic analysis of 270 patients with various histiocytoses, Durham, Rodrigo, Picarsic, and colleagues identified a previously unknown set of potential driver mutations in genes encoding receptor tyrosine kinases, including activating mutations in *CSF1R* (encoding CSF1R, also known as M-CSF) and rearrangements in *RET* and *ALK*. In one case, whole-exome sequencing of tissue samples from one-year-old monozygotic, monochorionic, diamniotic twins with the histiocytic disorder systemic juvenile xanthogranuloma revealed identical in-frame deletions in *CSF1R* in skin lesions, but not in blood or fingernails. The presence of identical *CSF1R* mutations in disease lesions but not blood or fingernails of the twins supports the idea that a *CSF1R*-mutant extra-embryonic yolk-sac precursor was the originator of the tumors. This finding aligns with the results of a recent mouse study and does not support the alternative explanation that the origin of the malignant clone was a bone marrow–derived myeloid cell that arose in one twin and spread to the other through vascular anastomoses. In addition to identifying a potential developmental origin for a histiocytic disorder, the group tested whether the presence of certain potential driver mutations was predictive of response to corresponding drugs. Notably, substantial and sustained responses were seen in patients positive for the *BICD2–BRAF*, *KIF5B–ALK*, or *NCOA4–RET* rearrangements treated with the MEK1/2 inhibitor trametinib, the ALK inhibitor crizotinib, or the RET inhibitor selpercatinib, respectively. These results highlight the potential value of genomic analysis in patients with treatment-refractory histiocytoses and provide preliminary evidence supporting treatments that may be of value in patient populations bearing specific types of mutations. Additionally, further investigation to determine whether the developmental origin of other histiocytic disorders matches that described here for systemic juvenile xanthogranuloma would be of interest. ■

Durham BH, Rodrigo EL, Picarsic J, Abramson D, Rotemberg V, De Munck S, et al. Activating mutations in CSF1R and additional receptor tyrosine kinases in histiocytic neoplasms. Nat Med 2019;25:1839–42.

AACR American Association for Cancer Research

CANCER DISCOVERY

Mutations in Receptor Tyrosine Kinases Drive Histiocytic Disorders

Cancer Discov 2020;10:11. Published OnlineFirst December 6, 2019.