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 G1 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.


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 potential histiocytosis-driving mutations. 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 disease originator.

A Small-Molecule Drug Targeting STAT3 Causes Tumor Regression in Mice


Updated version Access the most recent version of this article at:
doi:10.1158/2159-8290.CD-RW2019-175

E-mail alerts Sign up to receive free email-alerts related to this article or journal.

Reprints and Subscriptions To order reprints of this article or to subscribe to the journal, contact the AACR Publications Department at pubs@aacr.org.

Permissions To request permission to re-use all or part of this article, use this link http://cancerdiscovery.aacrjournals.org/content/10/1/11.1. Click on "Request Permissions" which will take you to the Copyright Clearance Center's (CCC) Rightslink site.