(SD2020-085) Targeting RBP-Prss23 Binding Interaction For Myc-Dependent Cancer Therapy. Therapeutic for Myc-dependent cancer.

Tech ID: 32885 / UC Case 2020-085-1

BACKGROUND

Considering the versatile functions of m6A in various physiological processes, it is thus not surprising to find links between m6A and numerous human diseases; many originated from mutations or single nucleotide polymorphisms (SNPs) of cognate factors of m6A. The linkages between m6A and numerous cancer types have been indicated in reports that include stomach cancer, prostate cancer, breast cancer, pancreatic cancer, kidney cancer, mesothelioma, sarcoma, and leukaemia

C-MYC(MYC) was among of the earliest described human oncogenes identified and is now recognized as the primary driver in oncogenic transformation and maintenance of cancer gene expression programs in a broad spectrum of cancer types where cells become “addicted” and dependent on MYC for survival. MYC transcript stability is coordinately regulated by RNA-binding proteins that both positively and negatively affect its half-life. Several RBPs interacting with m6A-modified RNA become upregulated in cancer, and are required for cellular growth, survival and invasion of cancer cells. Thus, Myc regulates cellular function and survival in part by modulating RNA metabolism and is itself controlled posttranscriptionally by RBPs.

There have been conflicting findings regarding the function of YTHDF2 in cancer. For example, loss of YTHDF2 sensitizes acute myeloid leukemia (AML) cells to TNF-induced apoptosis, while overexpression of YTHDF2 in hepatocellular carcinoma (HCC) represses cell proliferation and growth by destabilizing EGFR mRNA [9, 10]. Moreover, the direct YTHDF2 target RNAs have yet to be defined in the mammary epithelial or in human breast cancer. It is unknown if the mechanism in other cancer types may be attributed to YTHDF2-Prss23 regulation. Existing art includes US20100104501A1 patent, characterizing Prss23 as a biomarker, therapeutic and diagnostic target. The invention involves compounds which bind to and/or inhibit the activity of PRSS23, which is the opposite of what we have determined is required to trigger apoptosis in Myc-dependent cancer.

There are no current findings suggesting intervention of the YTHDF2-Prss23 binding interaction as a cancer therapeutic.

TECHNOLOGY DESCRIPTION

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OTHER INFORMATION

KEYWORDS

CRISPR screening, MYC-driven cancer, N6-methyladenosine, RNA-binding protein, STAMP, YTHDF2, scRNA-seq

CATEGORIZED AS

- Medical
  - Disease: Cancer
  - Therapeutics

RELATED CASES

2020-085-1

UC San Diego researchers have identified a binding interaction between N-6 Methyladenosine RNA Binding Protein 2 (YTHDF2) protein and Serine Protease 23 (PRSS23) transcript where YTHDF2 binds to m6A modified sites on the 3’ untranslated region (UTR) of Prss23. YTHDF2 selectively binds m6A modified sites on RNA and localizes target transcripts to mRNA decay sites for degradation by the CCR4-NOT deadenylase complex. We have shown in particular that abolishing this interaction triggers apoptosis in Myc-dependent breast cancer cells. Specifically, the lethality of YTHDF2 knockout was identified by RBP CRISPR/Cas9 screening in isogenic Myc-inducible human mammary epithelial cells and the binding interaction with Prss23 was identified by overlapping YTHDF2 eCLIP-seq, m6A-seq, and RNA-seq datasets in several human Myc-dependent breast cancer cell lines.

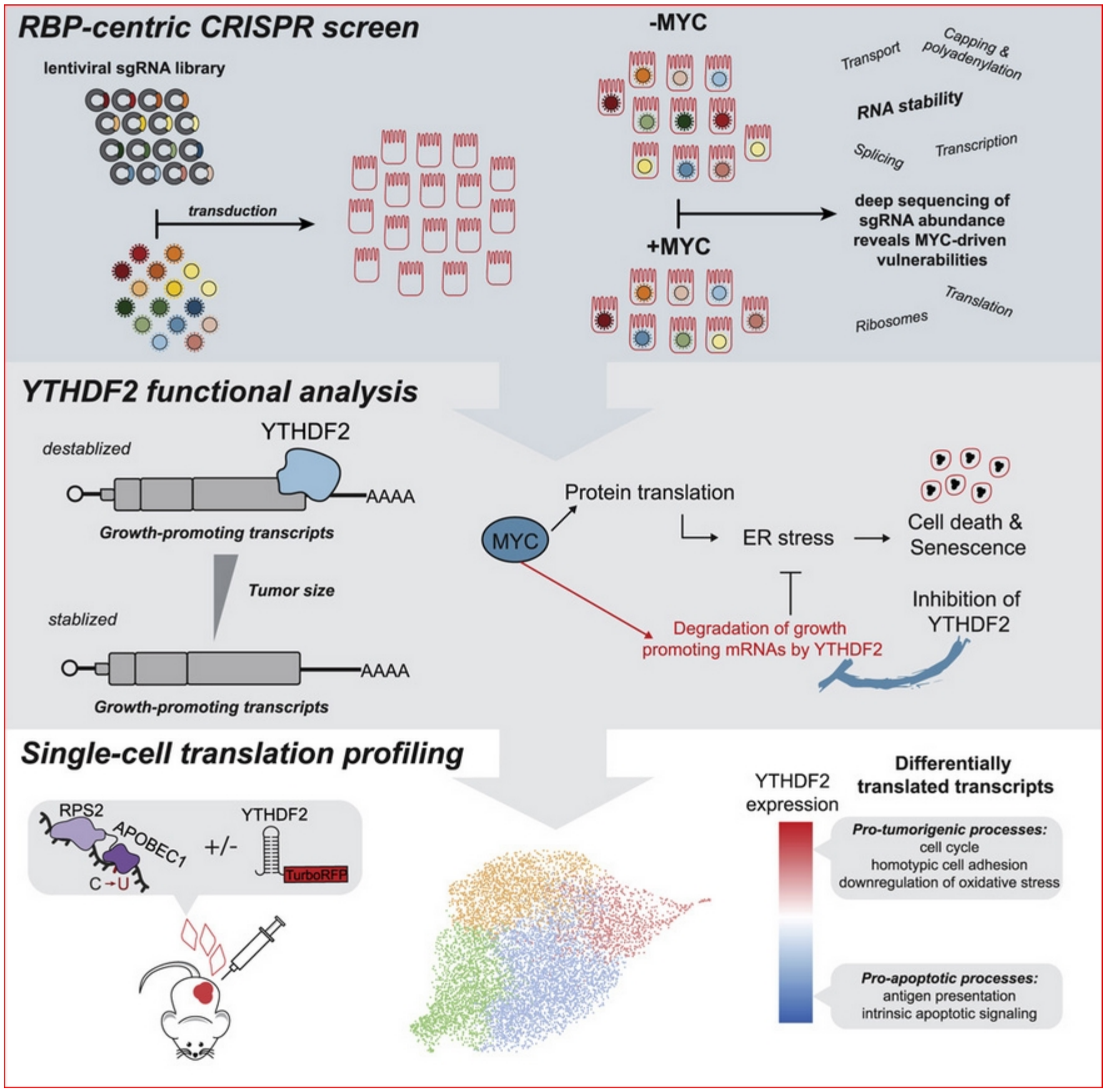
APPLICATIONS

Therapeutic for Myc-dependent cancer.

The role of RBPs in MYC-driven breast cancer was investigated by using an RBP-specific CRISPR-Cas9 screen. The screen yielded 57 cancer-supportive RBPs, that mostly had roles in mRNA stability and translation, of which at least 40 had not previously been implicated in the MYC pathway. As MYC overexpression in HMECs is used as an experimental model system, Einstein et al. importantly extended the validity of their findings by cross-referencing with The Cancer Genome Atlas where, remarkably, 67% of their candidates were found to be highly expressed in triple-negative breast cancer (TNBC). YTHDF2 was among a small group of RBPs for which, in addition, decreased expression correlated with patient survival, highlighting that targeting this protein could provide new therapeutic avenues.

ADVANTAGES

from the publication:



STATE OF DEVELOPMENT

UC researchers have confirmed that shRNA-mediated depletion of YTHDF2 causes apoptosis in Myc-dependent cancer cells and we have achieved rescue of the apoptotic phenotype by depleting both YTHDF2 and PRSS23, showing that ablation of newly synthesized PRSS23 protein is sufficient for restoring normal levels of translation initiation by western blot and cell proliferation by time-laspe imaging.

INTELLECTUAL PROPERTY INFO

RELATED MATERIALS

► Einstein JM, Perelis M, Chaim IA, Meena JK, Nussbacher JK, Tankka AT, Yee BA, Li H, Madrigal AA, Neill NJ, Shankar A, Tyagi S, Westbrook TF, Yeo GW. Inhibition of YTHDF2 triggers proteotoxic cell death in MYC-driven breast cancer. Mol Cell. 2021 Aug 5;81(15):3048-3064.e9. doi: 10.1016/j.molcel.2021.06.014. Epub 2021 Jul 2. PMID: 34216543; PMCID: PMC8359670. - 07/02/2021

PATENT STATUS

Patent Pending

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