DOI:10.1093/jnci/dju365
First published online November 27, 2014

EDITORIAL

MAX-ing Out MYC: A Novel Small Molecule Inhibitor Against MYC-Dependent Tumors

Iok In Christine Chio*, Georgi Yordanov*, David Tuveson

*Authors contributed equally to this work.

Correspondence to: David A. Tuveson, MD, PhD, Cold Spring Harbor Laboratory, 1 Bungtown Road, Cold Spring Harbor, NY 11724 (e-mail: dtuveson@cshl.edu).

The Myc oncogene features prominently in human cancers, being overexpressed or activated in more than 70% of malignancies (1). It is a basic helix-loop-helix (bHLH) transcription factor that lies at the crossroads of many growth-promoting signal transduction and bioenergetic pathways (2). Genetic studies in animal models have revealed that suppression of Myc activation leads to rapid tumor shrinkage caused by inhibition of cell proliferation, induction of senescence, and apoptosis, as well as remodeling of the tumor microenvironment (3). This phenomenon, coined “oncogene addiction,” has been demonstrated to be a feature of tumors even when MYC is not the initiating oncogenic event, thus rendering MYC a coveted therapeutic target (4).

Insights into the regulation of MYC expression and function have shed light on the development of novel therapies. BET bromodomain-containing proteins were found to be potent regulators of MYC expression through association with active enhancer elements. This has led to the development of the BET bromodomain inhibitor, JQ1, as a powerful therapeutic in murine models of hematological malignancies (5,6). Unfortunately, JQ1 exhibits limited effect in other cancer types, possibly because of lineage-dependent differences in the epigenetic landscape or different mechanisms that regulate MYC expression independent of enhancer activation (7). In parallel to regulating *MYC* expression, other efforts have focused on inhibiting MYC function. MYC is found to heterodimerize with another bHLH protein, MAX, to achieve gene activation by recruiting multiple coactivator complexes (8). Using a mutated version of the MYC bHLH domain (Omomyc) that acts in a dominant negative fashion to inhibit endogenous MYC-MAX interaction, it has been shown that MYC transcriptional activity can be abolished in vivo, resulting in the eradication of oncogenic *Kras*-driven lung adenocarcinoma in mice, with mild and fully reversible side effects (4). However, despite these promising results, none of the small molecule inhibitors of MYC-MAX dimerization developed thus far have demonstrated clinical efficacy, owing largely to short terminal half-life and rapid metabolism (9).

Pancreatic ductal adenocarcinoma (PDA) is an almost universally fatal disease and is one of the few cancers for which survival has not improved substantially over the past 40 years (10), despite extensive efforts in preclinical and clinical science. An activating mutation in *KRAS* is the most commonly encountered genetic perturbation (>90% of all cases) in PDA. However, KRAS is largely assumed to be undruggable because all attempts to target the activity of the oncoprotein directly have so far shown limited success in the clinic. For example, farnesyl- and geranyltransferase inhibitors, which block KRAS post-translational modifications and thus membrane localization, exhibited great potency in preclinical models, yet in clinical studies their activity was far less than anticipated, largely because of limited specificity and to innate resistance mechanisms (11). Other approaches that have emerged over the past years include small molecule inhibitors that block SOS-mediated nucleotide exchange and thus KRAS activation (12,13), *KRASG12C* inhibitors that allosterically shift the affinity of KRAS to favor the GDP state over the GTP state (14), as well as inhibitors that block the interaction between Kras and the prenyl-binding protein, PDEδ, to suppress oncogenic RAS signaling by altering its localization to endomembranes (15). Akin to farnesyl and geranyltransferase inhibitors, toxicity and adaptive resistance remain major hurdles for these approaches. The most promising strategies currently in clinical trials target downstream effector pathways of KRAS. Combination targeting of the Raf/MEK/ERK and PI3K/Akt effector pathways has been demonstrated to be required for effective inhibition of KRAS-dependent tumor growth (16). Interestingly, it has been reported that the Ras/Raf/ERK pathway stabilizes Myc by phosphorylation, thus extending its half-life (17). Moreover, using an embryonic stem cell based model of PDA, it was recently shown that c-Myc plays a major role in early PDA development (18). These data support the premise that targeting Myc may be a fruitful therapeutic strategy for Kras-driven PDA.

In the current issue of JNCI, Stellas et al. (19) report the identification of a novel small molecule inhibitor of MYC-MAX dimerization, which they name Mycro3. This inhibitor was shown to exhibit potent therapeutic efficacy in a highly aggressive mutant Kras-driven murine model of PDA. Continuous administration of Mycro3 to moribund mice led to prolonged survival and reduction in tumor size, while all control mice succumbed to the disease during the period of treatment. Similar results were also obtained in orthotopic xenografts of human PDA cell lines, as well as in murine models of lung and breast cancer, exemplifying the broad dependency of different tumor types on the *Myc* oncogene (19). Importantly, compared with previous studies of Myc inhibitors, Mycro3 showed improved pharmacokinetics and bioavailability in vivo. While promising, the authors also showed in their study that tumor cells were never fully eradicated upon continuous treatment with Mycro3. As such, further investigation into the nature of the resistant population as well as the mechanism of evasion will be imperative for successful clinical application.

Likewise, testing this drug in autochthonous murine models of PDA where Kras is activated at the endogenous level may better predict the efficacy of this drug in the human setting (20–22). Given that inhibition of Myc results in profound but reversible effects on regenerating tissues, metronomic administration of the drug, as opposed to the continuous treatment schedule used in the current study, should be assessed in the future to better evaluate drug efficacy (4).

In summary, the work by Stellas et al. (19) presents Mycro3 as a new Myc antagonist, and further preclinical and potentially clinical evaluation of this class of compounds are warranted as a new anticancer strategy.

References

1. Gabay M, Li Y, Felsher DW. MYC Activation Is a Hallmark of Cancer Initiation and Maintenance. *Cold Spring Harb Perspect Med*. 2014;4(6):a014241–a014241.
2. Dang CV. MYC on the Path to Cancer. *Cell*. 2012;149(1):22–35.
3. Sodir NM, Swigart LB, Karnezis AN, Hanahan D, Evan GI, Soucek L. Endogenous Myc maintains the tumor microenvironment. *Genes Dev*. 2011;25(9):907–916.
4. Soucek L, Whitfield JR, Sodir NM, et al. Inhibition of Myc family proteins eradicates KRas-driven lung cancer in mice. *Genes Dev*. 2013;27(5):504–513.
5. Delmore JE, Issa GC, Lemieux ME, et al. BET bromodomain inhibition as a therapeutic strategy to target c-Myc. *Cell*. 2011;146(6):904–917.
6. Zuber J, Shi J, Wang E, et al. RNAi screen identifies Brd4 as a therapeutic target in acute myeloid leukaemia. *Nature*. 2011;478(7370):524–528.
7. Lockwood WW, Zejnullahu K, Bradner JE, Varmus H. Sensitivity of human lung adenocarcinoma cell lines to targeted inhibition of BET epigenetic signaling proteins. *Proc Natl Acad Sci U S A*. 2012;109(47):19408–19413.
8. Amati B, Brooks MW, Levy N, Littlewood TD, Evan GI, Land H. Oncogenic activity of the c-Myc protein requires dimerization with Max. *Cell*. 1993;72(2):233–245.
9. Guo J, Parise R, Joseph E, et al. Efficacy, pharmacokinetics, tisssue distribution, and metabolism of the Myc–Max disruptor, 10058-F4 [Z,E]-5-[4-ethylbenzylidine]-2-thioxothiazolidin-4-one, in mice. *Cancer Chemother Pharmacol*. 2009;63(4):615–625.
10. Rahib L, Smith BD, Aizenberg R, Rosenzweig AB, Fleshman JM, Matrisian LM. Projecting Cancer Incidence and Deaths to 2030: The Unexpected Burden of Thyroid, Liver, and Pancreas Cancers in the United States. *Cancer Res*. 2014;74(11):2913–2921.
11. Berndt N, Hamilton AD, Sebti SM. Targeting protein prenylation for cancer therapy. *Nat Rev Cancer*. 2011;11(11):775–791.
12. Maurer T, Garrenton LS, Oh A, et al. Small-molecule ligands bind to a distinct pocket in Ras and inhibit SOS-mediated nucleotide exchange activity. *Proc Natl Acad Sci U S A*. 2012;109(14):5299–5304.
13. Sun Q, Burke JP, Phan J, et al. Discovery of Small Molecules that Bind to K-Ras and Inhibit Sos-Mediated Activation. *Angew Chem Int Ed Engl*. 2012;51(25):6140–6143.
14. Ostrem JM, Peters U, Sos ML, Wells JA, Shokat KM. K-Ras(G12C) inhibitors allosterically control GTP affinity and effector interactions. *Nature*. 2013;503(7477):548–551.
15. Zimmermann G, Papke B, Ismail S, et al. Small molecule inhibition of the KRAS-PDEδ interaction impairs oncogenic KRAS signalling. *Nature*. 2013;497(7451):638–642.
16. Zhong H, Sanchez C, Spitrzer D, et al. Synergistic effects of concurrent blockade of PI3K and MEK pathways in pancreatic cancer preclinical models. *PLoS ONE*. 2013;8(10):e77243.
17. Sears R. Multiple Ras-dependent phosphorylation pathways regulate Myc protein stability. *Genes Dev*. 2000;14(19):2501–2514.
18. Saborowski M, Saborowski A, Morris JP, et al. A modular and flexible ESC-based mouse model of pancreatic cancer. *Genes Dev*. 2014;28(1):85–97.
19. Stellas D, Szabolcs M, Koul S, et al. Therapeutic effects of anti-Myc drug on mouse pancreatic cancer. *J Natl Cancer Inst*. 2014;106(12):dju320 doi:10.1093/jnci/dju320.
20. Hingorani SR, Wang L, Multani AS, et al. Trp53R172H and KrasG12D cooperate to promote chromosomal instability and widely metastatic pancreatic ductal adenocarcinoma in mice. *Cancer Cell*. 2005;7(5):469–483.
21. Bardeesy N, Cheng K-H, Berger JH, et al. Smad4 is dispensable for normal pancreas development yet critical in progression and tumor biology of pancreas cancer. *Genes Dev*. 2006;20(22):3130–3146.
22. Ying H, Elpek KG, Vinjamoori A, et al. PTEN Is a Major Tumor Suppressor in Pancreatic Ductal Adenocarcinoma and Regulates an NF-κB–Cytokine Network. *Cancer Discovery*. 2011;1(2):158–169.

Funding

IICC is the Shirley Stein Fellow of the Damon Runyon Cancer Research Foundation (DRG-2165-13). GY is supported by the Leslie C. Quick, Jr fellowship at the Watson School of Biological Sciences. DT is supported by the Lustgarten Foundation for Pancreatic Cancer Research, the Cold Spring Harbor Laboratory Association, the Carcinoid Foundation, the STARR foundation (I7-A718), PCUK, DOD (W81XWH-13-PRCRP-IA), and the National Institutes of Health (5P30CA45508-26, 5P50CA101955-07, 1U10CA180944-01, and 5U01CA168409-3).

Notes

The authors declare no conflict of interest.

Affiliations of authors: Cold Spring Harbor Laboratory, Cold Spring Harbor, NY (IICC, GY, DT); Watson School of Biological Sciences, Cold Spring Harbor Laboratory, Cold Spring Harbor, NY (GY).