

Concepts to Target MYC in Pancreatic Cancer

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Abstract

Current data suggest that MYC is an important signaling hub and driver in pancreatic ductal adenocarcinoma (PDAC), a tumor entity with a strikingly poor prognosis. No targeted therapies with a meaningful clinical impact were successfully developed against PDAC so far. This points to

the need to establish novel concepts targeting the relevant drivers of PDAC, like KRAS or MYC. Here, we discuss recent developments of direct or indirect MYC inhibitors and their potential mode of action in PDAC. *Mol Cancer Ther*; 15(8); 1792–8. ©2016 AACR.

Introduction

Pancreatic ductal adenocarcinoma (PDAC) is a serious problem in modern medicine. This disease, which is usually driven by the mutated *KRAS* oncogene (1), is estimated to become the second leading cause of cancer-related deaths in the United States between the year 2020 and 2030 (2). The 5-year survival rates remain dismal at about 8%. Although the introduction of poly-chemotherapies represents a recent clinical advance, response rates continue to be unacceptable. In contrast to other solid tumors, where targeted therapies have been established, multiple trials testing targeted therapeutics failed so far.

Beyond the four main genetic lesions in *KRAS*, *CDKN2A*, *TP53*, and *SMAD4*, genetic heterogeneity, a hallmark of PDAC (3), is a crucial contributor toward the failure of therapies in the clinic. Beyond a few exceptions (4), it is unclear how genetic lesions translate into effective therapies, and deciphering vulnerabilities arising from genetic lesions remains challenging. Alternatively, defining and targeting nonredundant signaling hubs that are essential for maintaining PDAC is an attractive strategy. Current data suggest that the oncogenic transcription factor MYC (v-myc avian myelocytomatosis viral oncogene homolog) is such an important node in PDAC.

PDAC and the MYC Network

Copy-number variations (CNV) of the *MYC* gene are one of the most frequent genetic events among human cancers. Importantly, high-level CNVs of 8q24, harboring the *MYC* locus, were recently demonstrated to be solely associated with poor prognosis of PDAC patients (5). The transcription factor MYC heterodimerizes with MAX (MYC-associated factor X), and this dimer binds to E-box

sequences in the promoters of numerous genes. In addition to its activating functions, MYC can repress genes by association with the zinc-finger transcription factor MIZ-1 (Myc interacting zinc-finger 1; ref. 6). MYC alone is sufficient to initiate tumors and to drive tumor progression in the pancreas *in vivo* (5, 7–10). Furthermore, compelling evidence exists that MYC is an essential downstream effector of oncogenic *KRAS* in the pancreas (11–14). MYC expression is controlled at several layers in PDAC (15). In preneoplastic states of the disease, MYC can sense the signal from a *Kras*^{G12D}-induced autocrine loop, transmitted by the activated EGFR (14). The Notch pathway, in particular *Notch2*, acts upstream of MYC in a *Kras*^{G12D}-driven mouse model of PDAC (16). Furthermore, MYC expression is controlled by the PI3K signaling (17) or the canonical *KRAS*-ERK signaling (18, 19) pathways in PDAC (15). Together, MYC is an integrator of several important signaling pathways and therefore an attractive therapeutic target. Such a note is underscored by recent transcriptome-based subtyping of human PDACs. Here, Bailey and colleagues demonstrated the existence of four subtypes of PDAC: (i) the squamous subtype, (ii) the pancreatic progenitor subtype, (iii) the immunogenic subtype, and (iv) the aberrantly differentiated endocrine exocrine subtype (20). The squamous subtype of the disease, which overlaps with the quasi-mesenchymal subtype defined by Collisson and colleagues (21), is characterized by an activated MYC pathway (20) and the poorest outcome (20–22). These observations moreover reinforce MYC being a relevant driver in PDAC and argue that MYC targeting strategies are needed.

The potential of MYC as an emerging marker to stratify patients toward specific therapies was recently discussed (23). Here, we will focus onto current concepts how to target MYC with a special emphasis onto pathways with evidence of importance in PDAC.

A Therapeutic Window to Inhibit MYC

On account of the fact that MYC is involved in many aspects of the biology of normal cells, potent MYC inhibitors might be associated with pronounced toxicities. However, *in vivo* data argue that systemic MYC inhibition is possible. Omomyc is a dominant-negative variant of MYC with substitutions of four amino acids (E57T, E64I, R79Q, R71N) which is able to form heterodimers with wild-type MYC (24). This interaction interferes with the binding of MYC to MAX, leading to inhibition of E-box-dependent transcription. Only mild and reversible toxicities in tissues with a high proliferation index were observed upon systemic MYC

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inhibition by Omomyc in mice, arguing for an existing therapeutic window (25). Importantly, inhibiting MYC in a Kras-driven lung cancer model eradicates tumors even in a p53-deficient background (26). Excitingly, no resistance mechanism toward Omomyc-dependent inhibition of MYC was detected. Therefore, MYC seems to be a nonredundant node of nononcogenic addiction, at least in certain tumor entities in mice (26). Whether potent genetic inhibition of MYC is effective in murine Kras-driven mouse models of PDAC *in vivo* is not published so far. In a PDAC model, relying on the switchable expression of MYC in the murine pancreas *in vivo*, it was recently demonstrated that MYC inhibition induced a complete macroscopic tumor regression (9), well in line with the assumption that these tumor cells are addicted to MYC. Yet, dormant, nonproliferative tumor cells were detected in this particular model upon MYC withdrawal and tumor regression. These tumor cells, able to survive under a MYC withdrawn condition, can give rise to recurrent cancers (9, 27). Such observations have important implications for the development of potent MYC inhibitors for the treatment of PDAC. Considering that targeted therapies commonly fail to eradicate residual disease in humans, it is currently unclear how far the astonishing efficacy of MYC inhibition in some animal models can be extrapolated to human PDAC. Furthermore, tumor dormancy/tumor cell quiescence has to be considered as a potential escape mechanism upon potent MYC inhibition in the pancreatic context. Considering the currently increasing response rates toward therapies in the clinic, demonstration that quiescence upon a targeted therapeutic approach occurs in the pancreatic context points also to the need to decipher the molecular underpinnings of such processes in detail. Furthermore, concepts to exploit tumor cell quiescence therapeutically must be developed. In addition, Sancho and colleagues connected MYC expression levels to cellular states with different tumor-forming capacity (28). Low MYC expression was connected to stemness features, and such capabilities were increased upon inhibition of MYC in the investigated PDAC stem cell models (28). Therefore, such circuits might also limit efficacy of certain MYC inhibitors.

Nevertheless, cure upon MYC inhibition observed in the above-mentioned lung cancer mouse model clearly contributed to stimulate the development of MYC inhibitors (Fig. 1). Drugs targeting MYC directly or indirectly are currently under development (29, 30).

Targeting MYC Directly

The current molecular inhibitors in oncology, like kinases or lysine deacetylases, exhibit enzymatic activities and commonly the catalytically active site is targeted. In contrast, inhibiting protein–protein interaction is a challenging task. However, drugs like nutlin, inhibiting interaction of p53 with its E3 ubiquitin ligase MDM2, or ABT-737, acting as death-inducing drug by mimicking the prodeath BH3-only proteins, demonstrate that manipulating protein–protein interactions is feasible. The basic helix-loop-helix (bHLH) leucine zipper (LZ) dimerization domain of MYC is intrinsically disordered, lacking a clearly fixed and defined three-dimensional structure in solution. Thus, the development of direct MYC/MAX dimerization inhibitors remains difficult. The pharmacokinetic and pharmacodynamic properties of dimerization inhibitors were recently summarized in an excellent review article (29). Among several compounds targeting MYC/MAX dimerization, we will review the Mycro3 and

10058-F4 inhibitors, because data from PDAC models are available. Mycro3, based onto a pyrazolo[1,5- α]pyrimidine core structure, was shown to inhibit MYC/MAX dimerization in fluorescence polarization assays, electrophoretic mobility shift assays, and reporter-gene assays (31). Functionally, Mycro3 was shown to inhibit proliferation of MYC-dependent osteosarcoma cells, but not PC12 cells, a cell line defective for MAX (31). Conversely, Mycro3 is more active in the MYC-proficient rat fibroblast cell line TGR1 compared with its MYC knockout derivative H015.19 (32). In a monotherapeutic trial, Mycro3 blocks proliferation and induces apoptosis as well as distinct tumor shrinkage in a very aggressive murine Kras^{G12D}-driven PDAC model *in vivo* (32). Furthermore, using orthotopic xenotransplants of human PDAC cell lines, evidence was provided that Mycro3 is also active in human disease models (32). Despite inducing a clear reduction of the tumor burden, no obvious side effects of Mycro3 were reported (32).

In addition to Mycro3, the MYC/MAX dimerization inhibitor 10058-F4 (33) was tested in PDAC models. 10058-F4 interacts with the amino acids 402–409 of the C-terminal bHLH-LZ domain of MYC (34), thereby preventing MYC/MAX dimerization. *In vitro*, 10058-F4 was shown to impair proliferation and to induce apoptosis of human PDAC cells (35). However, *in vivo*, no activity of 10058-F4 was detected toward s.c. transplanted human Panc1 cells, but 10058-F4 synergistically induced apoptosis together with gemcitabine (35). These data might be explained by the inappropriate pharmacokinetics of 10058-F4 observed *in vivo* (36). However, recent data demonstrate that such problems can be solved, and a nanoparticle-based delivery of a 10058-F4 prodrug was demonstrated to improve survival in an *in vivo* model for multiple myeloma (37). Although direct MYC inhibitors are far from being clinically tested, especially the abovementioned Mycro3 study argues that direct MYC inhibitors should be further developed, improved and tested in PDAC. In contrast to the complete extinction of Kras-driven lung tumors by Omomyc (26), residual cancer remains upon Mycro3 treatment (32), and therefore, it will be important to study Mycro3 resistance or escape mechanisms. Transcriptome profiles show that MYC gene signatures were inhibited in Mycro3-treated murine PDACs (32), arguing for a direct inhibition of MYC. Although Mycro3 does not affect the dimerization of the activator protein 1 (AP-1) transcription factor (31), potential off-target effects of Mycro3 were not systematically evaluated and therefore might contribute to the remarkable effects of Mycro3 *in vivo*. Other small-molecule inhibitors, in addition to Mycro3 and 10058-F4, are currently under development. For example, synthetic α -helix mimetic MYC inhibitors (Fig. 1) prevent binding of MYC to E-box sequences without disrupting the MYC/MAX dimer (38). However, these inhibitors were not tested in PDAC models so far.

In addition to small-molecule inhibitors of MYC, further strategies based on antisense oligonucleotides or RNAi offer additional opportunities to target MYC directly. Such attempts are important to consider, because they already entered clinical trials. Here, a dicer-substrate short-interfering RNA targeting MYC, which is delivered via lipid nanoparticles, is currently under investigation in a phase I trial including different solid cancer entities (39).

MYC recruitment to DNA is controlled by mechanisms beyond MYC/MAX dimerization (40). Therefore, such molecular processes also offer the opportunity to target MYC. For the pancreas, bromodomain PHD transcription factor (BPTF) needs selective attention. BPTF is a component of the NURF (ATP-dependent

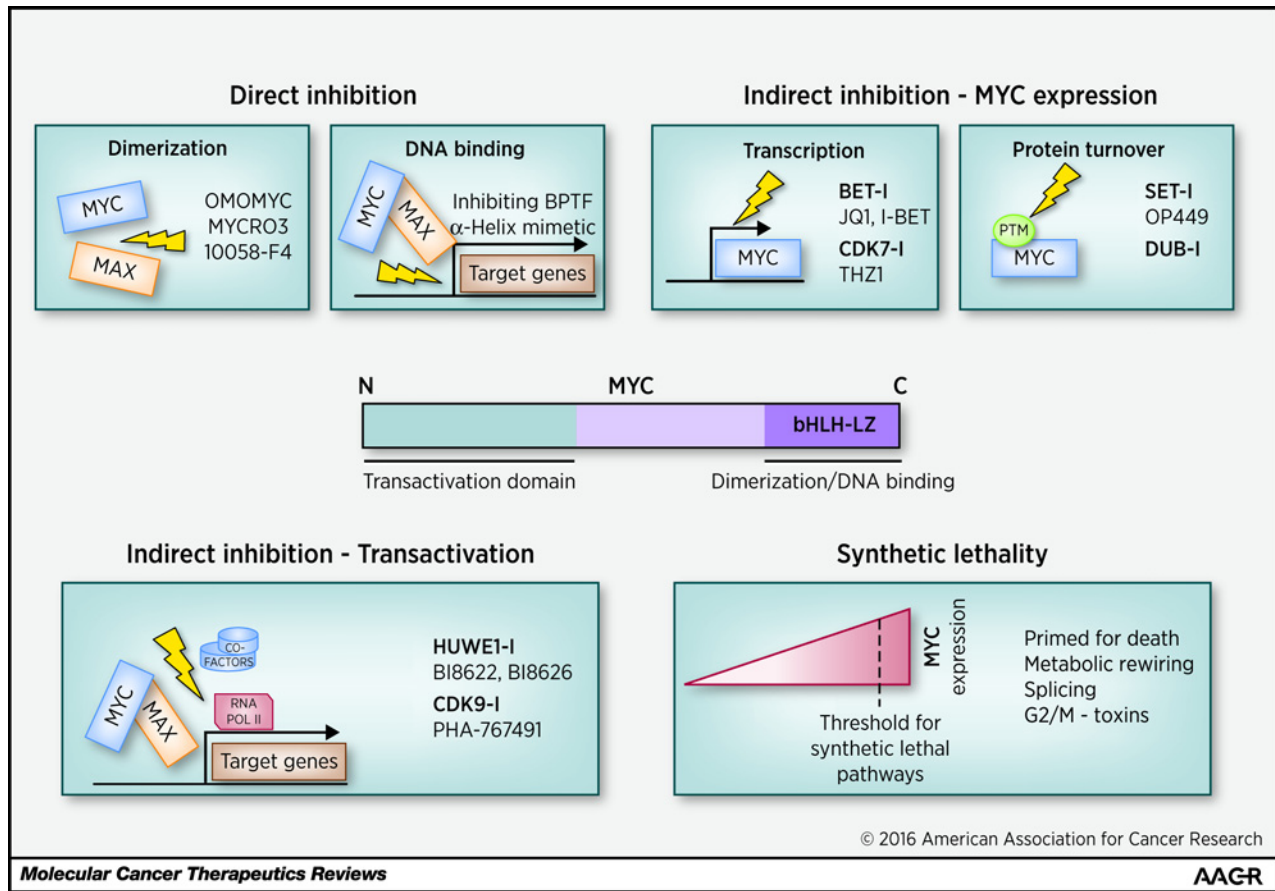


Figure 1. Ways to target MYC. Depicted is MYC with the N-terminal transactivation domain (TAD) and the C-terminal dimerization and DNA-binding domain (bHLH-LZ). Direct MYC inhibitors block the dimerization of MYC and MAX or interfere with binding of the dimer to DNA *in cis*. Indirect Inhibitors interfere with MYC expression at the level of transcription or protein turnover, or they target the transactivation function of MYC. Furthermore, PDACs with deregulated MYC are characterized by specific traits, which may include an exploitable primed for death phenotype, the MYC-dependent metabolic rewiring, vulnerabilities associated with the RNA processing machinery, or therapeutics targeting the G₂-M phase of the cell cycle, beyond others.

nucleosome-remodeling factor) complex, which functions in nucleosome sliding. There is evidence that MYC exists in a complex with BPTF (41). Interfering with BPTF expression reduces MYC binding *in cis* and impairs expression of a specific genetic MYC subnetwork (41). Importantly, reducing BPTF expression impairs MYC-driven carcinogenesis in the pancreas *in vivo* (41). Thus, molecular machines regulating MYC recruitment to DNA offer a further opportunity to target MYC and a MYC subnetwork. Therefore, molecular mechanisms controlling MYC recruitment should be deciphered in further research.

Targeting MYC Indirectly

In a simplistic view, indirect MYC inhibitors fall into two categories. First, inhibitors that reduce MYC protein expression or, second, inhibitors that interfere with MYC-dependent activation of genes, so called downstream inhibitors (Fig. 1). A plethora of drugs reduce the expression of MYC and also in PDAC numerous inhibitors (15), including inhibitors of main driver pathways, like the MEK (mitogen-activated protein kinase kinase)-ERK (18, 42) and PI3K (17) pathways, regulate MYC protein expres-

sion. Although MYC degradation occurring after long-term ERK inhibition in PDAC was connected to senescence (42), it is unclear in most instances whether the detected regulation of MYC is a bystander effect or responsible/directly connected to the drug-induced cell fate decision. Because several ways to interfere with MYC function in PDAC were recently summarized (15), we will only review new concepts with high potential for translational science.

In 2011, an unbiased RNAi screen identified the bromodomain (BRD) and extra terminal domain (BET) family member and transcriptional coactivator BRD-containing 4 (BRD4) as a main regulator of MYC expression in acute myeloid leukemia (43). The BET family consists of BRD2, BRD3, BRD4, and BRDT. These proteins recognize and bind to acetylated lysines of histones. Therefore, such proteins recruit factors needed for active transcription, like the positive transcriptional elongation factor pTEFb. Accordingly, BET proteins couple histone acetylation to sites of active transcription (44). The tight relationship of BRD4 to MYC fostered the development of several BET inhibitors [BET-I; e.g., JQ1 (45) or I-BET (46); Fig. 1], which already entered clinical trials (47). BET-I reduced MYC expression and show activity in

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MYC-dependent hematologic malignancies (43, 48). In such models, BRD4 directly regulates transcription of MYC, irrespectively whether MYC transcription is controlled by the endogenous promoter/enhancer or upon translocation by the immunoglobulin heavy-chain enhancer (44). However, the molecular mode of action of BET-I is highly context dependent and not always correlated with effects onto MYC. For instance, in non-small cell lung cancers, the efficacy of the BET-I JQ1 is connected to the AP-1 family member FOS-like antigen 1 (FOSL1) but not to MYC (49). These context-specific effects are currently explained by the observation that genes regulated by so-called "super-enhancers," enhancers with high level of BRD4 recruitment spanning up to several kilo base pairs of DNA, are particular sensitive to BET-I (50). Usage of super-enhancers, which are limited in number in a certain cancer cell and control the expression of key oncogenic driver genes, is highly context dependent. The context specificity is not only observed between different tumors, but also within a given tumor entity. In line, transcriptome profiles of BET-I-treated cells demonstrated a dramatic heterogeneous response, even in tumors of the same entity (51). Furthermore, in breast cancer models, the regulation of MYC mRNA in response to BET-I does not discriminate between sensitive and insensitive lines, further pointing to the highly context-dependent function of MYC in the response toward these kinds of drugs (52).

In PDAC *in vitro* models, BET-I reduced the growth of cells cultured in collagen (53). However, JQ1 controls MYC not in all of the investigated PDAC cell lines, and here, FOSL1 and HMGA2 (high-mobility group AT-hook 2) were shown to be additional oncogenic drivers downregulated upon BET inhibition (53). In human PDAC patient-derived xenotransplants (PDX), JQ1 showed activity (54). It was demonstrated that JQ1 reduced proliferation and a distinct reduction in tumor growth in 4 of 5 individual subcutaneous PDX models (54). Although MYC mRNA levels were slightly decreased upon the treatment with JQ1 *in vivo*, no regulation of MYC protein expression was described (54). In contrast, expression of the cell-cycle regulator CDC25B (cell division cycle 25B) was diminished, and this molecular event closely correlated with therapeutic efficacy (54), arguing that CDC25B is the relevant BET-I-sensitive driver in the investigated model. In addition to the human PDX models, JQ1 activity was recently demonstrated in a genetically engineered PDAC mouse model (GEMM). Here, MYC and proinflammatory pathways were blocked by JQ1 (12). In sum, preclinical data argue that BET-I-based therapies should be further developed. Such a note is further corroborated by the outstanding and robust synergism between JQ1 and the HDAC inhibitor (HDAC-I) SAHA observed in different GEMMs as well as human PDX *in vivo* models (12). However, the role of MYC in such therapeutic concepts needs to be defined, and the current data argue that BET-I acts in MYC-dependent as well as in MYC-independent modalities.

Given the efficacy of JQ1 as well as JQ1/HDAC-I combinations in PDAC models, BET-I resistance mechanisms must be considered. Interestingly, it has been shown that one resistance mechanism was associated with the upregulation of WNT signaling, and this process is needed to restore the expression of important drivers initially downregulated by BET-I, including MYC (51). Consistently, in cell-based PDAC models, activation of the WNT signaling pathway confers resistance, whereas WNT inhibition was synergistic with the JQ1 response (51).

In a recent unbiased screen for drugs with high efficacy in small-cell lung cancers, a group of top-scoring drugs, including BET-I

and cyclin-dependent kinase 7-inhibitors (CDK7-I), was connected to the transcriptional machinery (55). The general transcription factor IIIH (TFIIH) complex contains CDK7 and regulates RNA polymerase II (RNA Pol II) by phosphorylation of the C-terminal domain at Ser5 and Ser7, needed for transcriptional initiation and pausing. As BET-I, the CDK7-I THZ1 (56) was shown to target especially oncogenic driver genes controlled by super-enhancers (55–58), including MYCN or MYC. Therefore, inhibition of CDK7 is a further possibility to target MYC-enhanced programs (Fig. 1). Efficacy of THZ1 in PDAC and the role of MYC in the response have not been reported yet.

In normal cells, MYC is a short-lived protein with a half-life of 20 to 30 minutes, and its turnover is also deregulated in cancers (59). Therefore, accelerating the degradation is an alternative way to target MYC. Protein stability of MYC is regulated by tightly connected phosphorylation/dephosphorylation events, which are connected to ubiquitination/deubiquitination cycles (59). Phosphorylation at the serine 62 (S62) residue of the N-terminal MYC homology box I by kinases like ERK increases its stability and activity. The priming phosphorylation at S62 enables glycogen synthase kinase 3 β (GSK3 β) to phosphorylate threonine 58 (T58) to finalize MYC signaling. T58-phosphorylated MYC is targeted by the tumor-suppressive protein phosphatase 2A (PP2A) for S62 dephosphorylation with consecutive recruitment of the E3 ubiquitin ligase Skp1-Cullin1-F-box (SCF), containing the F-box protein FBXW7 (F-box and WD repeat domain containing 7) as target recognizing subunit. This leads to MYC ubiquitination and subsequently to its proteasomal degradation. PP2A action can be counteracted by endogenous PP2A inhibitors, like CIP2A (cancerous inhibitor of PP2A) and SET (IGAAD, PHAPII, I-2PP2A, TAF-I), which can directly interact with the N-terminus of MYC to prevent PP2A-dependent dephosphorylation of S62. Endogenous PP2A inhibitors are overexpressed in cancers, including PDAC (60, 61). Functionally interfering with CIP2A and SET expression reduces S62 phosphorylation of MYC and its expression in PDAC cells (ref. 61; Fig. 1). Importantly, a SET inhibitor (SET-I), OP449 (62), able to reactivate the PP2A activity to MYC and suitable for *in vivo* application is available (63). When OP449 was tested in human PDAC cells, four of seven tested cell lines were sensitive. Using two sensitive cell lines in s.c. xenotransplants, the *in vivo* efficacy of OP449 was demonstrated (61).

FBXW7 controls cellular programs, such as apoptosis and cell cycle, by targeting various oncoproteins, including MYC, NOTCH1, JUN, Cyclin E, and MCL1. In a subset of PDACs, FBXW7 is mutated or not expressed at all (64, 65). In addition to SCF^{FBXW7}, other E3 ligases such as SCF^{SKP2} contribute to the control of MYC (59). Ubiquitination is dynamic, and deubiquitinases (DUB) can revert and stabilize proteins. The ubiquitin-specific protease USP28 was the first DUB connected to MYC stability (66). Blocking USP28 expression leads to decreased MYC expression and proliferation of tumor cells (66), arguing that USP28 is a therapeutic target. Another recently identified DUB, USP36, was reported to target MYC in the nucleolus, thereby contributing to ribosomal RNA synthesis (67). Although inhibitors of DUBs, including USP28 inhibitors, for the treatment of cancer therapies are under development, they will target several relevant oncogenes in a specific context and again, the role of MYC in the cellular response must be determined.

In addition, the E3 ligase HUWE1 (MULE, HECTH9, ARF-BP1, LASU1, URE-B1) contributes to the regulation of MYC activity (68). HUWE1 was shown to ubiquitinate MYC, but this process

leads not always to changes in steady-state levels. In contrast to K48-linked ubiquitin, which is the signal for degradation, HUWE1 was shown to be able to induce K63-linked ubiquitination of MYC which is needed for transactivation of MYC target genes (68). Therefore, HUWE1 inhibitors may act downstream and prevent MYC-dependent transactivation of oncogenic programs. Indeed, HUWE1 inhibitors (BI8622 and BI8626) were recently developed (ref. 69; Fig. 1). Mechanistically, evidence was provided that HUWE1 inhibitors shift the activating MYC/MAX complex to a repressive MIZ1/MYC/MAX complex to deactivate a MYC-dependent oncogenic network (69), offering a further strategy to target MYC-addicted PDACs.

In addition to HUWE1 inhibitors, other mechanisms were recently proposed to interfere with MYC-dependent transactivation of oncogenic programs. There is evidence that MYC can act as a direct or indirect general amplifier of a pre-existent and context-specific oncogenic genetic network (40). MYC-dependent transcription needs the assembly of multiprotein complexes. Among others, such complexes include epigenetic writers, like histone-acetyltransferases (HAT), epigenetic readers, like BET proteins, or the basal transcription machinery, like the TATA box-binding protein (TBP; refs. 70–72). An important role for MYC in the release of the paused RNA Pol II at the proximal promoter of MYC-bound genes was demonstrated (73). Therefore, inhibition of processes bridging MYC to RNA Pol II can be used to inhibit MYC-dependent programs. MYC can interact and recruit the pTEFb factors cyclin T1 and CDK9 (72). CDK9 phosphorylates Ser2 of the C-terminal domain of RNA Pol II, needed for productive transcriptional elongation. Consistent with the idea that inhibition of MYC to RNA Pol II bridging/regulatory processes can be used to target MYC-dependent oncogenic programs, Huang and colleagues showed that pharmacologic inhibition of CDK9 by PHA-767491 (74) could be used as a therapeutic strategy for hepatocellular carcinomas with high MYC expression (ref. 75; Fig. 1). The negative correlation of MYC expression with the PHA-767491 IC₅₀ values was also observed in leukemias, lymphomas, and lung cancer models (75). Because a very basic mechanism of MYC and cancer biology is targeted, a similar approach might be useful for many cancers, including PDAC.

Conclusions

Development of improved compounds, directly targeting the MYC–MAX interaction with upgraded pharmacologic properties, should be continued, rigorously tested for specificity and off-target effects and also investigated as experimental drugs in PDAC models. Envision that such direct inhibitors will be available, it is important to study resistance mechanisms assuring survival of cancer cells with blocked MYC.

In addition to target MYC by direct and indirect inhibitors, alternative opportunities to exploit the biology of MYC at the therapeutic level exist. We have recently summarized MYC-associated vulnerabilities (synthetic lethality; Fig. 1) currently emerging in PDAC, which provide the option to develop subgroup-specific therapies (23). Such approaches are very important, because they offer the chance of direct translation with drugs

already used in the clinic. Beyond others, a primed for death phenotype (23, 76), the complex MYC-dependent rewiring of the metabolic program in PDAC (77), the dependency on proper splicing (78, 79), or vulnerabilities connected to the G₂–M-phase of the cell cycle (80) may provide therapeutic opportunities in PDAC (Fig. 1). Therefore, such synthetic lethal approaches can be used alternatively and combined to target MYC-addicted PDACs.

Extensive research in various GEMMs modeling different cancer types shows that MYC is an outstanding target (81). However, testing of these findings in novel human cancer models reflecting the whole heterogeneity spectrum of the disease is necessary. Here, the recent development of human organoid PDAC models (82, 83) will provide an appropriate platform to further develop MYC inhibitors and MYC-based therapeutic concepts in human disease models.

Currently, a fascinating new technology arises at the horizon with the potential to target the "undruggable" cancer drivers, which is based onto the recruitment of targeted proteins to E3 ligases. Winter and colleagues used a phthalimide-conjugated BET inhibitor as a proteolysis targeting chimera (PROTAC; ref. 84). PROTACs are bifunctional inhibitors that bind to the target of interest and in addition with a second moiety to E3 ligases (85). Thus, PROTACs hijack the intracellular protein ubiquitination machinery to degrade the target of interest (85). The phthalimide-conjugated BET-inhibitor dBET1 recruits cereblon, a protein of the cullin-RING ubiquitin ligase (CRL) complex, to ubiquitinate and degrade BRD4 and the BET family members BRD2 and BRD3 (84). In a murine xenograft model of MV4;11 leukemia cells, dBET1 leads to a degradation of BRD4 as well as to a reduction of MYC expression (84). The future development of potent drugs using the PROTAC approach might pave the way for a new class of direct MYC inhibitors.

It is clear that subtypes of PDAC revealing distinct genetic and molecular fundamentals have specific and unique therapeutic vulnerabilities. Understanding MYCs biology in tumor maintenance and the development of MYC-targeting strategies will be an important step toward precise medicines for MYC-addicted human PDACs.

Disclosure of Potential Conflicts of Interest

No potential conflicts of interest were disclosed.

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