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Review Article

Targeting MYC to Combat Pancreatic Cancer

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Abstract

Due to its invasiveness, heterogeneity and multiple-drug resistance, pancreatic ductal adenocarcinoma (PDAC) has been considered as a refractory malignant tumor. Although various studies have been conducted on the potential mechanisms that promote PDAC origination and metastasis, the research results and clinical translation to treat PDAC still needs improvement. With the development of individualized medicine and the implementation of gene sequencing, it has been confirmed that myelocytomatosis oncogene (MYC) contributes to poor prognosis in cancer cases. Furthermore, the deregulation of MYC exists in a majority of pancreatic cancer types, and is crucial for tumor cell proliferation and migration. Several recent studies have revealed the specific mechanisms of MYC in affecting PDAC, and clarified suppression of MYC as a promising therapeutic strategy. This review focused on emerging novel therapeutic strategies based on the direct or indirect targeting of MYC to combat PDAC.

Keywords: MYC; PDAC; Pancreatic cancer.

Abbreviations: ABBV-075, Mivebresib; AURKA, Aurora kinase A; BET, Bromo- and Extra-terminal; BETi, BET inhibitors; BPTF, bromodomain PHD finger-containing transcription factor; BRD4, Bromodomain-containing protein 4; CDK, Cyclin-dependent kinase; CDK1, Cyclin-dependent kinase 1; CDK2, Cyclin-dependent kinase 2; CDK7, Cyclin-dependent kinase 7; CDK9, cyclin-dependent kinase 9; CDKN2A, Cyclin-dependent kinase inhibitor 2A; c-Myc, Myc protein; CRD-BPs, Coding region instability determinant-binding proteins; CRDs, Coding region instability determinants; CTD, Carboxyterminal domain; DUB, Deubiquitinating enzyme; E1, Ubiquitin-activating enzyme; E2, Ubiquitin conjugating enzyme; E3, Ubiquitin ligase; ERAD, Endoplasmic reticulum-associated protein degradation; Fbw7, F-box and WD-40 domain protein 7; G4s, G-quadruplexes; Gem, Gemcitabine; HATs, Histone acetyltransferases; HCC, Hepatocellular carcinoma; HDAC, Histone deacetylase; HLH, Helix-loop-helix; HR, Homologous recombination; IGF2BP1, Insulin-like growth factor 2 mRNA-binding protein 1; KRAS, Kirsten Rat Sarcoma Viral Oncogene Homolog; L-Myc, Homologous proteins; LZ, Leucine zipper; MSI1, Musashi-1; MSI2, Musashi-2; MTOR, Mechanistic target of rapamycin; MYC, Myelocytomatosis oncogene; NFATc1, Nuclear factor of activated T cells c1; NGS, Next generation sequencing; NHE III1, Nuclease hypersensitive element III1; N-Myc, Homologous proteins; PARP, Polymerase; PARPi, PARP inhibitors; PDAC, Pancreatic ductal adenocarcinoma; PRMT5, Protein arginine methyltransferase gene 5; PROTAC, Proteolysis targeting chimera; RBP, RNA-binding proteins; RNAi, RNA interference; SAHA, Suberanilohydroxamic acid; SENPs, SUMO-specific proteases; SEs, Super-enhancers; Skp, S-phase kinase-association protein; SL, Synthetic lethality; SUMO, Small ubiquitin-like modifier; TAD, Transactivation domain; TAM, Tumor-associated macrophages; TME, Tumor microenvironment; TRRAP, Transformation-transactivation domain-associated protein; Ub, Ubiquitin; UPS, Ubiquitin-proteasome system.

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Introduction

The oncogene, myelocytomatosis oncogene (MYC), is a typical tumor-related gene involved in the origination and progression of a range of malignancies. Under normal conditions, the Myc protein (c-Myc), along with its homologous proteins (N-Myc, and L-Myc), are regulated by multiple intracellular signaling pathways. However, the MYC family members would be out of control during the period of tumorigenesis. With the development of next generation sequencing technology, approximately 50–60% of tumors have been detected with the upregulation of MYC expression.[1,2] The deregulation of MYC genes involves two major mechanisms: the activation of the KRAS/ERK pathway and the depression of the TGF-β/Smad4 pathway.[3,4] In addition, the abnormal activation of the intracellular signal network would converge on the MYC overexpression or protein stabilization, and confer the Myc-deregulated phenotype to cells. MYC plays an important role in malignant changes through gene amplification and translocation, mRNA upregulation, protein stabilization, the cell cycle, *etc*.[5] Furthermore, MYC promotes the aggressiveness of tumors by enhancing the expression of genetic materials, the bio-function of proteins, the proliferation of cancer cells, and energy metabolism (Fig. 1).[6–9] Moreover, MYC induces the conversion to tumor stem cells, and adapts cancer cells to the tumor microenvironment (TME) by stimulating cancer-associated fibroblasts and facilitating immune evasion.[10,11] MYC-driven cancers harbor a poor prognosis with an elevated probability of drug resistance and post-operation recurrence.[1] As a result, the deregulation of c-Myc is a harmful mutation

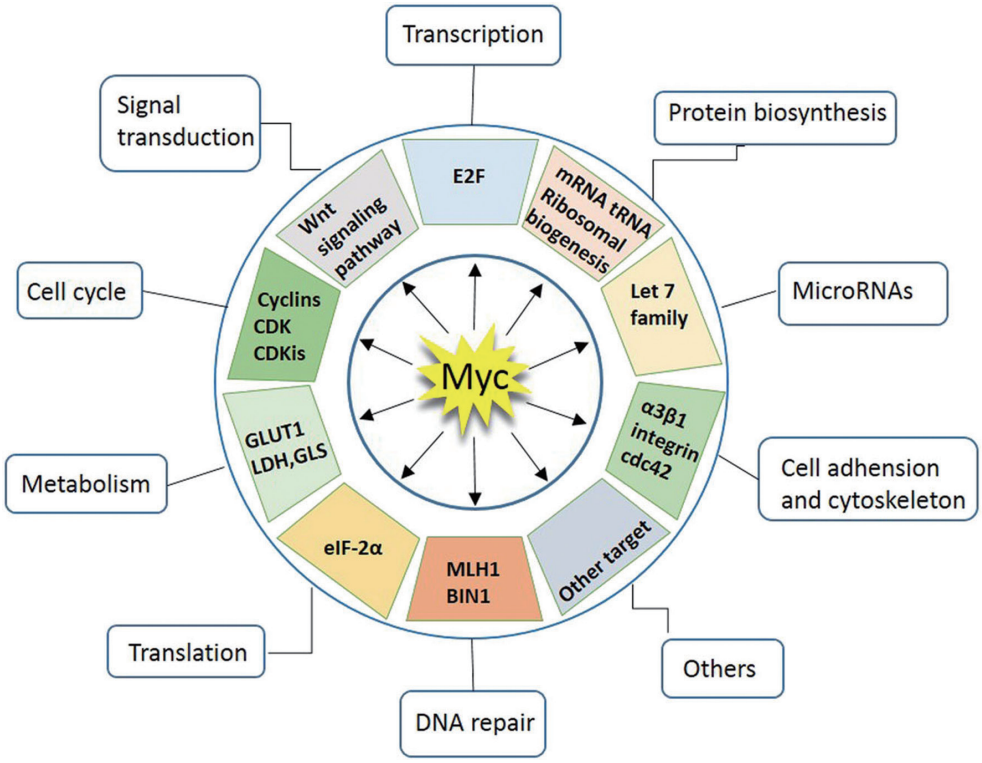

Fig. 1. Spectrum of cellular functions regulated by MYC. Reproduced from Reference 9 with permission from Springer Nature, Copyright 2018. MYC has interactions with a wide range of biomolecules, profoundly influencing cellular activities, including gene expression, DNA repair and genome stability, cell cycle and proliferation, energy metabolism, signal transduction, cell movement, *etc*. The deregulation of these processes together contribute to the tumorigenesis and development of pancreatic cancer.

that elevates the level of tumor-related gene expression, regardless of whether it was the previous transcriptional target.

Pancreatic ductal adenocarcinoma (PDAC) has been marked as one of the most challenging cancer types, which is characterized by dormant symptoms, high heterogeneity, and easy metastasis. Compared to other tumors, PDAC is basically resistant to traditional non-surgical therapy. Hence, the estimated 5-year survival rate for PDAC is approximately 5–10%.[12] Although various studies have been conducted on the potential mechanisms that promote PDAC origination and metastasis, the research results and clinical translation to treat PDAC still need to be improved. It has been reported that the rate of mutation of MYC can reach as high as 42% in advanced PDAC.[13] Given the fact that personalized treatment works in MYC-driven leucocythemia, breast cancer and other solid tumors, new therapeutic approaches for PDAC that target MYC would have a promising future. However, the research progress for the discovery of MYC inhibitors has not been smooth, because MYC is "undruggable". In particular, c-Myc has three critical domains (Fig. 2): (1) the amino-terminal domain, harbors conserved Myc box I and II, which are essential for the transactivation of

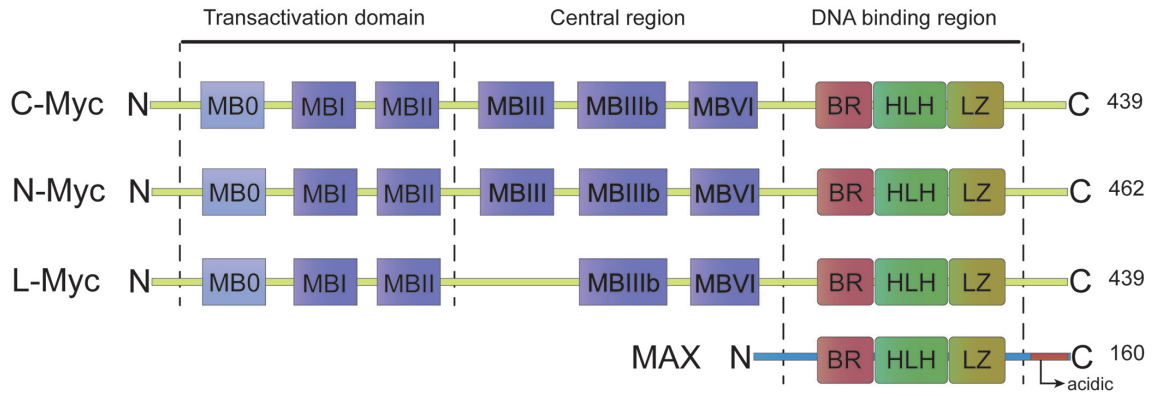

Fig. 2. Structure of MYC proteins and MAX. MYC has three functional regions: the transaction region, the central region, and the DNA binding region. Notably, the basic-region/helix-loop-helix/leucine-zipper motif, which also exists in MAX, is critical for DNA-protein interactions. MB: Myc box. BR: basic region. HLH: helix-loop-helix. LZ: leucine zipper.

Myc target genes; (2) the basic helix-loop-helix (HLH) DNA binding domain; (3) the carboxyterminal domain (CTD), comprises of the Myc leucine zipper (LZ) domain. The Myc itself, as a transcription factor, has no specific binding site for small molecules or targeted drugs to directly inhibit its activity. In addition, specific monoclonal antibodies are unable to target MYC, because it is located inside the cell nucleus.[14] In order to overcome these obstacles, alternative methods of indirectly targeting MYC are being deeply explored.

Since recent studies have revealed that in a wide range of aspects, MYC facilitates PDAC tumorigenesis and development, and clarified the suppression of MYC as a promising therapeutic strategy, various *in vivo* or *in vitro* researches are being undertaken. The present review focused on emerging novel therapeutic strategies based on the direct or indirect targeting of MYC to combat PDAC.

MYC in PDAC

The abnormal activation of MYC is a key event in PDAC onset and progression. MYC overexpression occurs in up to 42% of advanced PDAC, impressively demonstrating the putative oncogenic impact of this transcription factor.[13,15] The most common type of mutation is gene amplification, with a frequency of 12.8% in pancreatic cancer patients. It has been reported that the amplification of MYC is associated with worse survival in PDAC patients, especially for the adenosquamous subtype.[16] As a major upstream promoter of MYC, KRAS mutation occurs in approximately 30% of all human tumors, and this can reach as high as 90% in PDAC.[17] PDAC develops from pancreatic intraepithelial neoplasia, in which the KRAS proto-oncogene is mutated and progresses to malignant PDAC through multiple mechanisms that involve different transcription factors, such as Myc, CDKN2A (p16), SMAD4 and TP53. Based on its prominent role in acinar cell growth and differentiation, MYC has become a prime candidate for executing the KRAS-driven neoplastic transformation in the pancreas. Evidence has revealed that the function of c-Myc is highly dependent on the dose and cellular profile, as well as the recently demonstrated ability to reprogram somatic cells into a pluripotent stem cell-like state.[18] In other words, MYC overexpression is a sign of malignant growth, inducing stem cells to self-update, and preventing cellular senescence and differentiation. In addition, MYC contributes to the glucometabolic process in PDAC tumor cells, which prevents tumor cells from reaching a depleted nutrient state, and promotes tumor growth and metastasis.[7] Several new attempts have also revealed that MYC participates in epigenetic modification: MYC bides the specific region of the target gene, and simultaneously gathers chromatin remodeling co-factors in promoter regions.[19,20] The regulation of some epigenetic modifiers that remodel the entire chromatin structure has been confirmed to have connections with PDAC development. To some extent, chromatin-associated proteins play an important role in MYC-driven PDAC, bringing new insight to MYC-associated vulnerabilities. Furthermore, MYC confers resistance to multiple targeted therapies, highlighting the need for research on MYC-targeted therapy.[21–23]

Indirect targeting of MYC

Considering its pathogenesis process and practical value, the alternative approaches in indirectly targeting MYC in MYC-related PDAC can basically be divided into six classifications: (1) targeting the MYC transcription; (2) targeting the MYC mRNA translation; (3) targeting the MYC stability; (4) targeting the MYC-MAX interaction; (5) targeting the accessibility of MYC to downstream genes; (6) gene synthetic lethality (Table 1, Fig. 3).

Targeting the MYC gene transcription

The inhibition of MYC transcription can be divided into two categories: (1) to block upstream pathways that drive MYC transcription; (2) to suppress the transcription at the DNA level, including stabilizing the structure of the G-quadruplex (G4) and hindering the assembly of the transcription complex.

TGF-β-related inhibitors

Multiple mechanisms participate in MYC transactivation in its promoter regions. For instance, NF-κB directly works by combining with the MYC promoter, and the β-catenin/TCF4 complexes take effect in the MYC enhancer, in order to activate the MYC promoter.[24–26] In contrast, the TGF-β/Smad4 pathway acts as a negative regulator for the MYC transcription promoter.[27] However, due to the internal dysfunction or external interference towards the Smad family, the TGF-β signal can sometimes transform from a cancer-suppression element to a cancer-promoting element. It has been reported that the SMAD gene is deleted or mutated in over 50% of human PDACs.[28] Hence, inhibitors LY2109761 and FK506, which target switched TGF-β and the interference factor-calcium responsive nuclear factor of activated T cell c1 (NFATc1), respectively, were exploited, and these primarily demonstrated the ability to inhibit PDAC cell proliferation and growth in experiments *in vitro*.[29]

TGF-β can also modulate the MYC expression through non-SMAD-signaling. A recent research demonstrated the high levels of c-Myc expression in tumor tissues in advanced PDAC cases through the non-SMAD TGF-β signaling pathway.[30] In particular, this phenomenon is tightly connected with the interaction between TGF-β and tumor-associated macrophages (TAM). Furthermore, its subsequent study revealed that the use of galunisertib (a kind of TGF-β receptor inhibitor) plus gemcitabine can remarkably decrease the c-Myc expression. In the past few years, anti-TGF-β-based therapies for PDAC have made significant progress. TGF-β inhibitors, such as galunisertib and AP12009, have recently completed the phase I clinical trials, but the results have not been posted.

Stabilization of G-quadruplexes

G4s are four-stranded, non-canonical secondary structures formed by guanine-rich DNA sequences. The structure of a G-quartet is formed by Hoogsteen hydrogen-bonded guanines and core cation coordinated to oxygen atoms.[31] Studies have indicated that G4s participate in multiple genetic bioactions, both on physiological and pathological conditions, similar to genome stability or overexpression. Experimental data has revealed that G4s are inclined to generate during tumorigenesis. Reasonably, as a cancer-related gene with a high frequency of mutation, MYC has been confirmed with this quadruplex near its promoter region, which is called, nuclease hypersensitive element III1 (NHE III1, also known as the CT element). Preventing MYC transcription by stabilizing G4 is a feasible approach. The main binders for G4 are small-molecule substances with high affinity, either synthetic or natural, such as QN1. These ligands provide multiple innovative options for

Table 1. Examples of candidate inhibitors that directly or indirectly target MYC in PDAC

General mode of action	Target	Compound	Phase	Trial number	Reference
Targeting the MYC transcription	TGF-β	LY2109761	Pre-clinical		29
	G-quadruplex	CM03	Pre-clinical		32
	G-quadruplex	Porphyrin-1/2	Pre-clinical		
	Super enhancer	GZ17-6.02	Phase I	NCT03775525	36
	Super enhancer	Minnelide	Phase II	NCT04896073	
	BRD4	OTX015/MK-8628	Phase I	NCT02259114	
	BRD4	GSK2820151	Phase I	NCT02630251	
	BRD4	INCB057643	Phase I/II	NCT02711137	
	BRD4	Entinostat	Phase I	NCT03925428	
	BRD4	ARV-825	Pre-clinical		43
	BRD4	JQ1	Pre-clinical		42,46,47
	CDK7	THZ1	Pre-clinical		56
Targeting the MYC mRNA translation	EIF5A	Silvestrol	Pre-clinical		59
	Musashi-2	KLF4	Pre-clinical		63
	IGF2BP1	LINC00261	Pre-clinical		66
Interfering with the MYC stability	Skp2	Curcumin	Pre-clinical		72
	Skp2	Arsenic trioxide	Pre-clinical		74
	DUB	PR-619	Pre-clinical		79
	CDK4/6	Palbociclib	Phase I	NCT03065062; NCT04870034; NCT02178436	
	CDK2	Dinaciclib	Phase I	NCT01783171	83,84
	ERK1/2	Ulixertinib	Phase I	NCT04566393	
	AURKA	Alisertib	Phase I	NCT01924260	
	AURKA	AS703569	Phase I	NCT01097512	
	AURKA	CCT137690	Pre-clinical		91
Targeting the MYC/MAX heterodimer	MYC-MAX dimerization	Mycro3	Pre-clinical		95
	MYC/MAX	Omomyc	Phase I/II	NCT04808362	
Blocking the access of MYC to genes	Pin1	Sulfopin	Pre-clinical		102
	p300	C646	Pre-clinical		112
Exploitation of synthetic lethality	PARP	Niraparib	Phase II		
	CDK1/5/7	Dinaciclib	Pre-clinical		83
	AURKB	VX-680	Pre-clinical		130

PDAC treatment. Ahmed *et al*. developed a variety of G4-binding molecules that update to CM03, a highly selective G4 regulator for PDAC, particularly for the gemcitabine-resistant type.[32] Furthermore, they reported that the combined use of CM03 and histone deacetylase (HDAC) inhibitor suberanilohydroxamic acid (SAHA) can improve the treatment efficacy in different subtypes of pancreatic cancers. The main function of CM03 is to stabilize G4s, thereby inhibiting the expression of downstream promoters. At the molecular level, CM03 can aggravate DNA damage, while at the cell level, this can induce cancer cell arrest and apoptosis. Based on this, the addition of HDACi can lead to more generations of G4s through the epigenetic modification of the chromatin

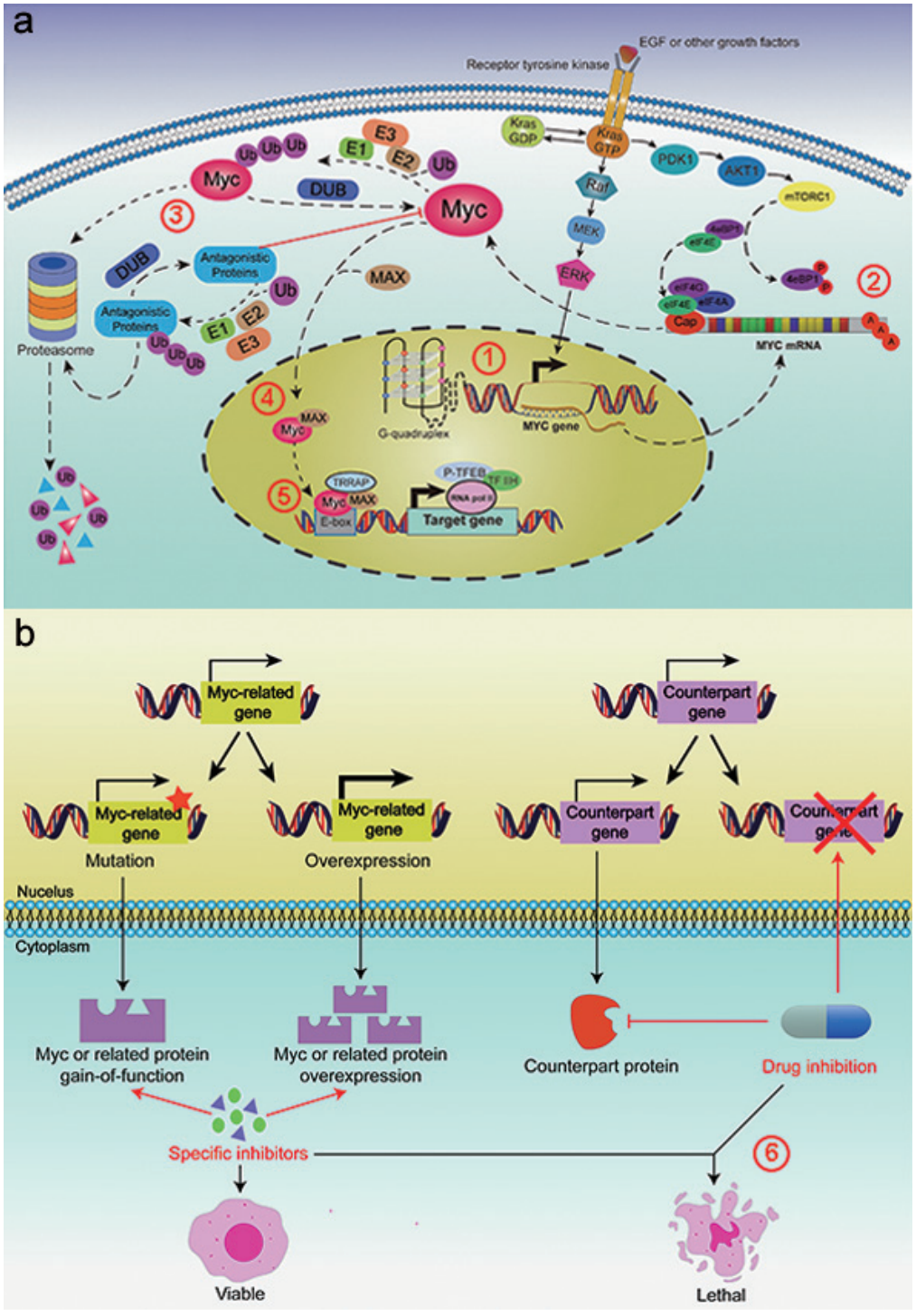

Fig. 3. Alternative approaches to indirectly target MYC. (a) MYC deregulation or loss-of-function by reducing its expression or oncogenic activity: (1) suppressing the transcriptional process of MYC by stabilizing the G-quadruplex structure of genome or blockading the signal transduction from MYC to RNA polymerase (2) suppressing the translational process by interfering with translation initiation factors; (3) regulating the stability and degradation of MYC, or its antagonistic proteins, majorly via the ubiquitin-proteasome pathway; (4) targeting the formation of the MYC/MAX heterodimer; (5) blocking the access of MYC or the MYC/MAX heterodimer to target genes. (b) The concept of synthetic lethality (SL) and the application to MYC-driven cancer. The mutation or overexpression of MYC-related genes, or the monotherapy targeting the corresponding protein it expresses can be viable for cancer cells due to the compensation of the counterpart protein. (6) SL was achieved through the combined pharmacological inhibition of two pathways. The star shape denotes the mutation. The thicker arrow denotes the increased expression. The red cross denotes the drug inhibition. The viable cell is depicted as an intact shape, and the inviable cell is depicted to be distorted and cracked.

structure, which has a synergic toxic effect. However, these DNA binding compounds remain controversial, in terms of safety. The biggest problem is the impairment or interference towards normal genomic functions. In the application of G4-binding molecule TMPyP4 in pancreatic cancer cells, it was reported that the *in vivo* side effect on normal cells significantly decreased.[33]

Super-enhancers (SEs)

In addition to the G4 area, which is the key to the activation of the MYC promoter, another special region in the genome named, super-enhancers (SEs), has recently drawn attention. As the name indicates, SEs are a large cluster of enhancers that generate high levels of transcription, and conform to cell type-specific biological processes.[34,35] A significant amount of data supports that SEs are closely correlated to the development of multiple cancers. It is possible that these tumor-related factors disrupt the regeneration and repair of normal signaling, and replaces this with SE-oriented plastic networks, inducing the aberrant switch in PDAC phenotype. A recent study used ChIP-Seq to identify the existence of SEs in PDAC cell lines, and the results revealed that the MYC gene region also contains such element. GZ17-6.02 attenuates the acetylation of SE genes, which leads to low levels of transcription factors, sonic hedgehog pathway proteins, and stem cell markers.[36] Hence, SEs can be a novel target site towards PDAC.

c-Myc interaction to RNA polymerase

Mammalian bromo- and extra-terminal (BET) proteins are essential for the initiation of transcription, and its role in recruiting co-regulatory factors onto the transcription platform, including the promoter and enhancer area. As a member of the BET superfamily, bromodomain-containing protein 4 (BRD4) has been well-acknowledged as an epigenetic modifier. In particular, BRD4 is involved in the genome-wide modulation of RNA transcription complex assembly and follow-up transcriptional elongation.[37] Concretely, with the high affinity to acetyl-lysin, BRD4 primarily triggers co-activator proteins, and locates onto hyperacetylated sites, similar to SEs, stimulating the phosphorylation of the carboxy-terminal domain of RNA polymerase II at serine 2.[38,39] Afterwards, RNA polymerase II is released from the region adjacent to the promoter, and facilitates the elongation.

JQ1 is a typical bromodomain inhibitor that indiscriminately inhibits BRD2 and BRD4. By blocking the binding pocket of the apo crystal structure of the first bromodomain of BRD4, JQ1 inhibits the transcription of genes.[40] In addition, researches on hematological malignancies and solid tumors have supported the notion that decreasing the amount of BET bromodomains can lead to the downregulation of the MYC gene itself, as well as MYC target genes.[41] However, the long-term use of BET inhibitors (BETi), such as JQ1, either *in vitro* or *in vivo*, would lead to the problem of drug resistance. According to this, researchers are exerting efforts to exploit new technologies and improve BETi. Sun *et al*. successfully created a drug-delivery nanoplatform that co-delivers a photosensitizer and JQ1 to the combinatory photoimmunotherapy of PDAC.[42] Furthermore, a latest study revealed the advanced proteolysis-targeting chimera (PROTAC), ARV-825, which can dramatically break BRD4, in order to control the MYC expression level in PDAC.[43] PROTAC is a newly emerging method that renders the acceleration of drug exploitation towards "undruggable" MYC. The experimental data revealed that ARV-825 inhibits cancer cell activities, both in pancreatic cancer cell lines and spheroid models.

In clinical trials, an oral pan-inhibitor of BET, Mivebresib (ABBV-075), is initially undergoing in-human studies. The preliminary results indicated that this has a tolerable safety profile, and takes effect to some extent in PDAC. However, further observation is needed.[44] Other compounds that has entered the clinical trial stage include OTX015/MK-8628, GSK2820151, INCB057643, *etc*.

In addition, the deficiency in KDM6A, a histone H3K27me3 demethylase, confers to the sensitivity to BETi, such as JQ1, in PDAC.[45] BETi can restore the cell identity by suppressing the MYC pathway and decreasing the p63 level.[45] The combined inhibition of BET and histone deacetylases exerts synergistic effects in reducing cell viability, and this probably has a higher anti-tumor potency, when compared to monotherapy with JQ1.[46,47] Future investigations on therapeutics that target genes that regulate epigenetics remain intriguing.

Cyclin-dependent kinase 7 and 9 (CDK7 and CDK9)

In addition to the interference of the signal transduction from MYC to RNA polymerase by BETi, an alternative approach is to target the co-activator substrates in the MYC transcription process, such as CDK7 and CDK9. Different from typical cell-cycle cyclin-dependent kinases (CDKs), which are in charge of cell-cycle modulation, CDK7 and CDK9 have essential roles, particularly in the transcription process.[48,49] For the catalytic subunit of the transcription factor IIH complex and the positive transcription elongation factor P-TEFb, both are selective phosphokinases that target the CTD of RNA Pol II, and consequently affect the whole transcription process. It has been confirmed in multiple experimental models that targeting RNA Pol II-related CDKs can lead to the diverse alteration of cellular bio-behaviors.[50–52] As previously mentioned, MYC is an oncogene equipped with SEs that forcefully strengthens the transcriptional activity. Indeed, researchers have revealed the SE region is the major action site of CDK7 and CDK9, suggesting that this subtype of CDKs may be a rational target spot for MYC-driven cancers.[48] The most potent known CDK9 inhibitor is flavopiridol, which has cytotoxicity on chronic lymphocytic leukemia cells.[50] FIT039, a newly developed antiviral drug that inhibits CDK9 activity, has been reported to reduce the expression of E6 and E7 oncogenes in cervical cancer.[53] Since there is a high expression of CDK9 in pancreatic cancers, the inhibition of this kinase may also be applied in PDAC treatment.[54] Furthermore, a recent study innovatively utilized PROTAC 2 to selectively deplete CDK9 in pancreatic cancer cells, and the data revealed the moderate reduction of cell viability.[55] Similar results have also been observed in CDK7 inhibitors. By screening the epigenetic-related compound library, Lu *et al*. identified a specific CDK7 inhibitor, THZ1, which can induce the pronounced downregulation of gene transcription PDAC cell lines.[56] These findings provide a novel and promising therapeutic approach to refractory PDAC.

Targeting the MYC mRNA translation

Multiple signaling pathways gather together to finely regulate the MYC mRNA translation process, such as the phosphoinositid-3-kinase/mTOR, KRAS/PEAK, and WNT/β-actin pathways.[57] At the same time, these pathways are also closely correlated to the development of PDAC. Regulating different signaling pathways and related translation factors may be a potent method to alter the post-transcriptional processes of MYC, and the biological behaviors of tumors.

The EIF5A-PEAK1 pathway

In PDAC, KRAS is a common protooncogene with diverse functions in tumorigenesis. A recent study demonstrated that KRAS can regulate a wide range of MYC downstream pathways with the assistance of translation initiation factor eIF5A, including protein translation, cytoskeleton organization, and the cell cycle regulatory pathway.[58] In this process, the crucial co-worker is the focal adhesion kinase PEAK1, which transmits integrin and growth factor signals mediated by TME. The EIF5A-PEAK1 pathway has been confirmed to participate in various cancer entities. An *in vitro* experiment identified that transcription factors YAP1 and TAZ are the major targets of eIF5A-PEAK1 signaling. The interdiction of eIF5A-PEAK1 signaling in PDAC cells can inhibit the YAP/TAZ protein expression, thereby controlling the MYC mRNA translation to downregulate c-Myc levels. In contrast, the amplified eIF5A-PEAK1 signaling would upregulate the YAP1/TAZ levels, and confer stemness to pancreatic cells. Presumably, blocking the eIF5A-PEAK1-YAP/MYC pathway may effectively reduce tumorigenicity and tumor growth in PDAC. Silvestrol, an inhibitor of eIF4A, has been recently reported to repress the c-Myc expression in pancreatic cancer *in vitro* and *in vivo*.[59]

The AKT/mTOR pathway

In the human body, the Ser/Thr kinase mechanistic target of rapamycin (mTOR) is an important downstream target of the PI3K signaling pathway. mTOR plays important roles in numerous biological processes, including cell survival, growth, proliferation, gene expression, and the regulation of apoptosis, and MYC translation is no exception.[60] Furthermore, PI3K/AKT/mTOR signaling is often linked to drug tolerance and therapeutic resistance in pancreatic cancer. A study revealed that the inhibition of the mTOR pathway can induce tumor cell apoptosis and reduce oncogenic phenotypes, coupled with c-Myc downregulation.[21] Conversely, the reduction in c-Myc expression would increase the sensitivity of pancreatic cancer cells to mTOR inhibition. However, the directly targeting of mTOR remains as a historical challenge for some cancer types, especially in advanced PDAC. Despite this, there are substitute methods to target mTOR-related factors, such as eIF4A, AKT, PI3K, *etc*. A number of PI3K/AKT/mTOR pathway inhibitors are undergoing research at present, such as sapanisertib, vistusertib, gedatolisib, *etc*.[61] Overall, as mentioned above, determining the weak links in the complex MYC translation regulatory network may offer new target spots in PDAC treatment.

The RNA binding protein

The abnormal epigenetic alteration of genome can induce human cancer. RNA-binding proteins (RBPs) are a special kind of proteins that are critical for maintaining the transcriptome through a series of post-transcriptional regulatory mechanisms.[62] RBP Musashi-1 (MSI1) and Musashi-2 (MSI2) were reported to exist in tumor cells, and these work as regulators of multiple critical biological processes relevant to cancer development.[63] Furthermore, MSI1 and MSI2 bind to the mRNA, and regulate the translation of oncogenic proteins, including MYC. Further studies on Musashi proteins have revealed that the suppression of KLF4, a transcriptional repressor of MSI2, can lead to MSI2 hyperexpression in PDAC cells, thereby enhancing the cancer progression and metastasis.[64] Targeting RBPs is a new treatment direction, but this remains challenging. Some preclinical researches are presently being undertaken, including those that use RNA interference (RNAi) technology, hoping to lead to further breakthroughs. Another group of RBPs, known as coding region instability determinant-binding proteins (CRD-BPs), is also essential for regulating MYC mRNA stability.[65] Coding region instability determinants (CRDs) are sequences within the mRNA with high affinity for CRD-BPs. CRD-BPs protect the mRNA from endonucleolytic attacks, thereby prolonging the mRNA half-life.[65] A member of CRD-BPs, insulin-like growth factor 2 mRNA-binding protein 1 (IGF2BP1), can equip the MYC mRNA with four protein subunits: HNRNPU, SYNCRIP, YBX1 and DHX9.46.[66] Experimental data has revealed that IGF2BP1 family proteins are significantly upregulated in pancreatic cancer cells, when compared to normal tissues. Due to this, researchers are developing inhibitors of IGF2BP1, or sequestering the binding to target proteins to treat cancer, including long noncoding RNAs, such as LINC00261.[67] The forced expression of LINC00261 can also inhibit cell glycolysis, and induce cell cycle arrest and apoptosis.

Targeting MYC protein stability

The ubiquitin-proteasome system (UPS)

c-Myc, as an evolutionarily conservative transcriptional regulator, is involved in regulating 15% of the gene expression in the human genome.[10] However, within the cell, c-Myc is an extremely unstable protein with a half-life of only 20-30 minutes, and is majorly degraded by the UPS.

The UPS is a crucial type of protein post-translational modification that participates in the degradation of more than 80% of proteins. The multistep cascade reaction consists of ubiquitin (Ub), ubiquitin-activating enzymes (E1), ubiquitin conjugating enzymes (E2), ubiquitin ligase (E3), deubiquitinating enzymes (DUB), and proteasomes.[68] After the target protein receives the ubiquitination signal, primarily with the participation of ATP, the glycine residues at the ubiquitin C-end form high energy thioester bonds to the cysteine residues of E1, which pass the activated ubiquitin molecules to E2. Under this action, in which E2 cooperates with E3s, the ubiquitin C-terminal is connected to the lysine residues of the substrate protein through an isopeptide bond. The last step is performed by proteasomes, which specifically identify and degrade the substrate protein. Deubiquitination is the reverse process of ubiquitination, which releases ubiquitin molecules, and regulates the stability, positioning and activation of the C-terminal between substrate proteins, and the poly-ubiquitin chain.

Studies conducted in recent years have revealed that ubiquitin connectors that regulate c-Myc stability can be classified into three categories, according to the binding domain: (1) E3 ubiquitin connectors that contain the really interesting new gene domain, such as the S-phase kinase-association protein (Skp); (2) E3 ubiquitin connectors that contain the homologous to E6AP C-terminus domain, such as F-box and WD-40 domain protein 7 (Fbw7), FBXO and β-Trcp; (3) E3 ubiquitin ligase that contains the U-box domain, and other E3 ubiquitin ligases.[69,70] Although Skp2 and Fbw7 belong to the F-box ubiquitin ligase protein family, both have different roles from each other. Skp2 has a dual action on c-Myc. This mediates the ubiquitination and degradation of c-Myc, and enhances the transcription of the target gene. Fbw7 can specially identify the phosphorylated T58 site of the c-Myc protein, thereby reducing the transcriptional activity of c-Myc, and regulating the ubiquitylation and degradation process. Furthermore, Fbw7 functions as a

tumor suppressor that downregulates c-Myc levels. A recent study on PDAC revealed that protein arginine methyltransferase gene 5 (PRMT5) can silence the expression of FBW7 and elevate the expression of c-Myc, thereby promoting cancer cell proliferation.[71] Hence, the inhibition of SP2 or protection of FBW7 may be used as a method to alter the c-Myc stability, and thereby treat pancreatic cancer.[72] The PRMT5/FBW7/c-Myc axis may be a novel therapeutic target for the treatment of pancreatic cancer.[71]

SKp2, as an oncoprotein itself, can control the cell proliferation by reducing p27, and enhance the transcriptional activity of c-Myc to promote more cells into the S stage and accelerate cell proliferation.[73] To date, main researches have achieved cancer inhibition by consuming the content of SKp2 or weakening its function. It has been reported that in PDAC, arsenic trioxide, as a Skp2 inhibitor, can downgrade the SKP2 expression, and inhibit cancer invasion and proliferation in *in vitro* models.[74]

Ubiquitination and deubiquitination regulate the dynamic balance of intracellular proteins. DUBs can hydrolyze the isopeptide bond between the ubiquitin and substrate, releasing ubiquitin molecules, and substrate proteins that lose the ubiquitin chain label signal, which is identified by 26S proteasomes, thereby maintaining stability. Present researches have revealed three major DUBs that contribute to c-Myc stabilization: USP28, USP7 and USP36. The first nucleoplastic DUB identified to connect with c-Myc is USP28. However, there is a lack of direct interaction between these. USP28 indirectly acts with c-Myc through ubiquitin ligase Fbw7α, which weakens the activity of Fbw7α and indirectly regulates the stability of c-Myc. USP28 may interact with the WD40 repeat sequence, and be a substrate of Fbw7. Within these, the S62 and T58 sites of c-Myc are in turn phosphorylated as recognition binding sites of Fbw7, and mutations in the T58 and S62 sites would affect the interaction between c-Myc, and Fbw7α and USP28, thereby regulating the stability and function of c-Myc.[75,76] Recent studies have identified more deubiquitinases that mediate the MYC-driven PDAC oncogenesis and progression. USP22 was identified to indirectly stabilize c-Myc through the selective regulation of the NFAT protein.[77] In addition, USP22 can suppress the immune infiltration and immunotherapy sensitivity of pancreatic cancer.[78] Since USP22 has a relatively high expression in PDAC, this may be used as a new treatment approach. The combination of chemotherapy and DUB inhibitor PR-619 has been demonstrated to prevent chemoresistance by blocking the c-Myc pathway.[79]

The ERK1/2 inhibitor

Except for the ubiquitin system that regulates c-Myc protein stability, a novel study revealed that ERK1/2-dependent mechanisms can maintain MYC protein stability. The application of ERK1/2 inhibitors would result in the rapid proteasome-dependent loss of MYC proteins and suppression of PDAC growth through ERK1/2-dependent or non-dependent mechanisms.[4] It noteworthy that the degradation of MYC is independent of the PI3K-AKT-GSK 3 signaling or E3 ligase. However, under the control of the suppression-induced feedforward mechanism through the EGFR/SRC/ERK loop, this would result in ERK5 activation and the phosphorylation of S62, thereby preventing c-Myc degradation.[80] Targeted therapy for multiple links of this regulatory pathway may contribute to the treatment of pancreatic cancer, such as the simultaneous inhibition of ERK1/2 and ERK5. In addition, a recent study revealed that the transcription factor, SLUG, can confer the resistance to MEK1/2 inhibitors in pancreatic cancer by uncoupling tumor progression from RAF-MEK1/2-ERK1/2 signaling, paving a path for the development of new therapies against PDAC.[81]

Cyclin-dependent kinase (CDK)

Similarly, protein kinase CDK2 (formerly casein kinase II), is an enzyme engaged in multiple pathways of tumorigenesis, which can directly target c-Myc proteins. The phosphorylation by CDK2 frees Myc from the degradation induced by the ubiquitin system. Interestingly, CDK2 is regulated by the KRAS/ERK/Src/STAT3 signaling pathway, and is closely correlated to PDAC, which harbors a high variation rate of KRAS.[82] Hence, the idea of regulating CDK2 to destabilize MYC may make a breakthrough in the treatment of refractory pancreatic cancer. In addition to the acidic region and the nuclear localization sequence of the MYC protein (both are phosphorylated by CDK2), the transactivation domain (TAD) of MYC is a third region of phosphorylation.[57] Within the TAD, Ser-62 is one of the sites that have drawn particular attention. The kinases implicated in the phosphorylation of the Ser-62 site of TAD of MYC include cyclin-dependent kinase 1 (CDK1). These pathways together contribute to the post-translational modification of MYC, thereby impinging on its function. Dinaciclib, as a non-selective CDK inhibitor, has been proven to be toxic to pancreatic cancer cells, and inhibit the growth of tumors *in vivo*.[83,84] Furthermore, the suppression of CDK expression by blocking the ERK/Src/STAT3 pathway may also serve as an alternative remedy for PDAC treatment. This was demonstrated in the study conducted on Oxalidaceae, which is a tradition Korean plant medicine.[85]

Small ubiquitin-like modifier (SUMO)

Small ubiquitin-like modification is a newly discovered system similar to the UPS, which can modify post-translational proteins.[86] More than 3,000 proteins have been identified as SUMO in cells. SUMOylation is an important mechanism that regulates the biological function of intercellular proteins, thereby affecting the stability of proteins and interactions between proteins, maintaining the dynamic balance in the normal physiological and biochemical process of the human body, and playing a vital role in tumor oncogenesis and development. Furthermore, SUMOylation engages in a series of enzymatic cascade reactions that involve ubiquitin activating enzyme E1, ubiquitin conjugating enzyme E2 and ubiquitin ligase E3, in which E3 can modify specific substrate proteins. It has been identified that SUMO-specific proteases (SENPs) can not only catalyze the maturation of the SUMO precursor and complete the SUMO modification, but also mediate the de-SUMOylation of substrates during the metabolism of SUMO. When the dynamic balance of SUMOylation and de-SUMOylation is destroyed, both the abnormal expression of the SUMO protein and SENPs would lead to cellular dysfunction, which in turn, promotes the development of cancer. The abnormal expression of the SUMO protein or SENPs exist in various malignant tumors. The overall survival for PDAC with a high expression of SUMO protein or SENP remains low. A recent study conducted by Biederstädt *et al*. revealed that SUMO suppressors, such as ML-93, can induce G2/M phase arrest and cell death, and that SUMO inhibition is closely correlated to the hyperactivation of MYC, suggesting that SUMO inhibitor-based therapy can be a potential option for the treatment of advanced PDAC subtypes.[87] In recent years, SUMO1P3, one of the pseudogene-expressed lncRNAs originally observed in gastric cancer, has attracted the interest of researchers. It was found that compared with normal pancreatic tissues, SUMO1P3 is highly expressed in PDAC, and that its relative expression is closely correlated with the tumor size, lymph node metastasis, and TNM stage.[88] In addition, tapping SUMO1P3 inhibits the proliferation,

migration and invasion of pancreatic cancer cells, and may be associated with the epithelial-mesenchymal transition process.

Aurora kinase A (AURKA)

As a member of the Aurora family, which is activated via autophosphorylation, AURKA plays an essential role in carcinogenesis through the interaction with MYC.[89] Furthermore, AURKA forms a complex with N-Myc, protecting N-Myc from FBW7-mediated proteasomal degradation. In addition to Myc, a wide range of oncogenes, tumor suppressors and mitosis regulators have been presently identified as AURKA substrates.[90] Some small molecules that target AURKA have been exploited and included in preclinical trials for the treatment of different cancer types. A research on mouse models of PDAC revealed that the administration of CCT137690, an AURKA inhibitor, induced cancer cell death and tumor growth retardation *in vivo*, and reduced the phosphorylation of AURKA at the molecular level.[91] In addition, protein kinases SA16 and IB35 were identified to exhibit specific inhibitory activity towards PDK1 and Aurora kinase A, thereby reducing pancreatic cancer cell proliferation and colony formation.[92] AURKA might be a vulnerability for the treatment of pancreatic cancer.

Targeting the MYC-MAX heterodimer

MYC proteins are specifically characterized by the basic helix-loop-helix-leucine zipper region, where another synergistic protein, MAX, can bind and form a MYC-MAX complex.[57,93] In the MYC network, the homodimers of MYC or MAX proteins can bind to the original E-box in the promoters of MYC-targeted genes, and activate a wide range of gene expression, while MAX can also form a heterodimer transcription repressor with MXD. It is known that the loss of MAX in mice considerably weakens the carcinogenic effect of MYC, even during the over-transcription of oncogene MYC. Nevertheless, in prior systemic chemotherapy cells, MAX depletion has a positive effect on the expression of MYC family proteins, and the overexpression-induced cell growth effects were partially eliminated.[1] Overall, the MYC/MAX complex is a kind of efficient dimer that regulates cell proliferation, metabolism, differentiation and apoptosis, as well as tumorigenesis. The presently developed small molecular inhibitors, 10058-F4 and 10074-G5, have been shown through *in vitro* experiments to inhibit the formation of heterodimers of c-Myc and MAX.[94] However, the rapid degradation and poor distribution of these molecules *in vivo* prevent these from further playing a role. Mycro3, a molecule that inhibits c-Myc binding to MAX, has exhibited remarkable therapeutic effects in mouse PDAC models, rendering it a potential drug for MYC-driven PDAC.[95] In addition, several pioneering alternatives to regulate c-Myc are emerging. Omomyc, a dominant-negative allele of MYC, selectively prevents the MYC/MAX dimerization-dependent transcription by heterodimerizing with MYC or MAX.[96] In convertible transgenic mouse models, Omomyc exhibited a wide treatment window, independent of carcinogenic lesions or origin tissues, and induced only mild and reversible side effects in normal tissues.[97–99] Early after systemic administration, Omomyc quickly reached the tumor site, successfully inhibited the target, reduced the tumor grade, and promoted disease withdrawal. At present, Spanish scholars have generated Omomyc for lung cancer, and this has entered clinical trials.[98] In pancreatic cancer, this requires further exploration. Experiments are presently being undertaken, and the results would foster further translational research.

Targeting the access of MYC to downstream genes

MYC acts as a transcription factor. After the binding of MYC to MAX, the complex needs to locate onto the chromosome segment around the target gene, which requires the participation of many co-activation molecules, in order to achieve the accurate positioning of the dimer, and change the chromatin into a structure conducive to binding. In particular, the first problem to be addressed is the nuclear localization of MYC/MAX, since most of the MYC target genes are located within the nucleus, including some tumor-related genes. Pin1, a prolyl isomerase that interacts with substrates that contain phospho-Ser/Thr-Pro, regulates the function of these substrates via the cis-trans isomerization of peptide bonds.[100] It has been shown that Pin1 can regulate the conformation of the MYC protein by phosphorylating serine 62, and inducing this to dynamically evolve with spatio-temporal changes. These changes are in favor of the nuclear localization of c-Myc, thereby initiating its role on the transcription of target genes at the chromatin level. Furthermore, it has been reported that Pin1 maintains proliferation signals by enhancing almost 50 cancer-related genes or growth promotion factors, as well as repressing tumor inhibitors or growth suppressors, making it an attractive focus to simultaneously block multiple cancer-driven pathways.[101] Recently, Pinch *et al*. developed a covalent inhibitor of Pin1, and validated its effectiveness to impair cell viability in PDAC cancer lines.[102] In mouse models of pancreatic cancer, Sulfopin induced the downregulation of c-Myc target genes, reduced the tumor progression, and improved the rate of survival.[103,104] Further studies are required to investigate the therapeutic effects and safety of Pin-dependent drugs, such as Sulfopin, in the treatment of pancreatic cancer.

As previously mentioned, in addition to its direct activating effects on genome, c-Myc can indirectly regulate the transcription of target genes with the assistance of different mediators, such as histone acetylase, chromatin regulatory proteins, basic transcription factors, and DNA methylase. More concretely, c-Myc participates in the positive transcriptional regulation via the protein-protein interaction in three ways: (1) interacting with BPTF to promote the transposition of nucleosomes and widen the space of the corresponding transcription sites; (2) recruiting histone acetyltransferases (HATs), and in turn, acetylate the adjacent regional histone; (3) recruiting transcription extension negative regulator p-TEFb. These mechanisms simultaneously or sequentially act together, improving chromatin accessibility, and promoting the accession of RNA polymerase.[105–107]

Previous studies have revealed that the inactivation of BPTF proteins (an important component of the nucleosome remodeling complex in pancreatic precancerous lesions) significantly delays tumor development and prolongs the survival of c-Myc overexpressing cells, and that the BPTF expression has a positive correlation with MYC gene signatures, implying that BPTF, as a key co-factor for c-Myc, performs a role in transcriptional initiation.[107] The pharmacological inhibition of BPTF with C620-0696, a potent inhibitor of BPTF, suppresses the expression of MYC in non-small cell lung cancer cells. However, its effectiveness in PDAC has not been clarified, to date.[108]

MYC can acetylate chromatin specific sites, and convene the associated co-factors to facilitate this process, such as transformation-transactivation domain-associated protein (TRRAP) or other HATs.

Located at 7q22.1 and highly conserved in evolution, TRRAP is a part of HAT complexes that form transcriptional activity centers together with other transcription factors, such as MYC, E2F1 and p53. In 1998, McMahon *et al*. reported that TRRAP interacts

with the c-Myc N terminus, and that the trans-dominant mutants of TRRAP or antisense RNA can prevent MYC-mediated oncogenesis. This shows that TRRAP is an important co-factor in the MYC-induced transcription factor pathway.[108] In a study conducted on hepatocellular carcinoma (HCC) cell lines, the researchers reported that the depletion of TRRAP or its cofactor, histone acetyltransferase KAT5, can induce the p53- or p21-independent senescence of HCC cells by activating mitotic genes.[109] Several HATs have been identified in favor of MYC-mediated transcriptional initiation, such as p300, gcn5 and CBP.[110,111] In PDAC, certain research progress in HAT inhibitors has been made, such as the selective p300 inhibitor C646.[112]

In addition to histone acetylation, MYC can also modulate histone methylation, thereby altering the transcriptional activity of target genes. A recent study revealed that MYC can interact with Dpy30, a major H3K4 methyltransferase complex, in order to facilitate chromatin accessibility.[113] Furthermore, the consumption of Dpy30 effectively blocked the MYC-dependent cell deterioration, without affecting normal cell growth. Epigenetic targets in the Dpy30 methylation pathway may be exploited for potential PDAC treatment. Furthermore, ASH2L, a subunit of KMT2 methyltransferase complex tri-methylating lysine 4 of histone H3, is also a binding co-factor for MYC. Chen *et al*. reported that circ-ASH2L is highly expressed in PDAC cells, is essential for tumorigenesis and tumor progression, and is probably associated with lymphatic invasion or TNM staging, suggesting that circ-ASH2L may be a useful biomarker for PDAC.[114] Inhibitors toward these kinds of histone methylases in PDAC treatment are undergoing experimental research.

Crucial for DNA replication, cyclin can be upregulated by c-Myc to promote its transcription. Since the CDK-cyclin complex can be suppressed by a number of factors, such as p21, to ensure smooth replication, c-Myc has also evolved its capacity as a negative transcription regulator. That is, c-Myc can broadly interact with functionally diverse transcription factors, notably Miz-1, a competitive inhibitor of p300. Miz-1 is a BTB/POZ domain zinc finger protein with 13 zinc fingers. Through its direct interaction with c-Myc, Miz-1 can recruit the MYC/MAX complex and prevent the recruitment of p300.[115] Since Miz-1 can promote the transcription of p21 and other genes, this specific inhibition method can better reduce the expression of proliferative negative factors, and promote proliferation.[116] It has been shown that c-Myc is very common in HCC to inhibit proliferative negative factors, such as p16 and p27.[117] Indeed, Miz-1 has been a MYC co-factor of concern, and its role on tumorigenesis is undergoing experimental research.

Synthetic lethality

MYC has been considered "undruggable" due to its lack of success in MYC-targeted related clinical therapy. Synthetic lethality (SL) is a promising approach to target MYC-dependent vulnerability in cancer. The concept of SL was first described in biogenetic research in the early 20th century. This means that the simultaneous inactivation of two specific nonlethal genes can cause cell death.[118] In 1997, Hartwell *et al*. proposed that synthetic lethal interactions can be exploited to identify new anticancer drug targets.[119] The use of synthetic death principles to develop new drugs lead to the identification of specific mutations in cancer cells and key counterpart genes to form SL (Fig. 3B). In theory, this approach can be translated into personalized therapy, and applied to any type of cancer mutation.

Recent studies have defined new categories of synthetic lethal interactions.[120] As predicted by Elledge *et al*., some of these synthetic lethal genes play an important role in the recovery from DNA replicational stress induced by specific oncogenes.[121] Broadly, SL can be divided into three categories: oncogene-addicted, non-oncogene-based, and drug-based SL. SL dependent on KRAS overexpression is the most common example of oncogene addiction.[122] Non-oncogene-based SL means that the depletion of a single gene increases the sensitivity of cancer cells to the inhibition of a complementary pathway. Drug-based SL is defined by the synergistic cytotoxicity with monotherapy by blocking compensatory pathways that sustain tumor growth. This new classification can lead to novel strategies for developing MYC-targeted drugs.

Since there is a high mutation rate of MYC in PDAC and a wide interaction network with other genes, drugs that target the MYC gene by exploiting the concept of SL would have a promising future. However, due to the difficulty of finding synthetic lethal candidates, these drugs are still undergoing research. A major account for this is the lack of overlap in results obtained from different synthetic lethal screenings. The conventional large-scale loss-of-function screening was dependent on RNAi technology, and there was a lack of specificity for high-throughput applications.[123] Fortunately, the adaptation of CRISPR technology for the large-scale mapping of genetic networks has made up for this defect. It can be observed that multiple druggable targets have been identified via genome-wide CRISPR screening in recent years.[124] Finally, big data and *in silico* platforms have been recently proposed as novel methods to elucidate potential therapeutic targets.[120]

The classic drugs developed according to the principle of SL are PARP inhibitors (PARPi). Poly (ADP-ribose) polymerase (PARP) transfers PAR or mono-ADP-ribose to the target proteins, thereby regulating a variety of biological activities, such as DNA replication and transcription.[125] In 2005, scholars from the UK reported the synthetic lethal interaction of PARP with breast cancer susceptibility genes BRCA1 and BRCA2.[126,127] Subsequently, researchers have reported that the efficacy of PARPi is not necessarily limited to germline-mutated BRCA1/2 tumors. Indeed, the sensitivity of cancer cells toward PARPi is closely associated with the defects in homologous recombination (HR) repair.[128] This means that PARPi may offer more treatment options for different cancer types, especially MYC-driven cancers with the instability of genome. After the first success in ovarian cancer in 2014, PARPi was extended to the treatment of pancreatic cancer. To date, there are over 30 registered PARPi agents for pancreatic cancer, and these are undergoing clinical trials.

At present, PARPi is confirmed to have a strong impact on MYC-mediated bioactivities. A study conducted by Carey *et al*. demonstrated that the combination of PARPi niraparib and dinaciclib (the inhibitor of the cyclin-dependent kinase, leading to the downregulation of MYC expression), yielded HR downregulation, and in turn, SL in MYC-driven triple-negative breast cancer cells, and in pancreatic, ovarian and colon cancers.[129] Similarly, Yang *et al*. reported that inhibitors of AURKB may be synergistic with MYC in the induction of a lethal form of autophagy.[130] A novel attempt was made by Lankes *et al*. to utilize genomics analysis and unbiased pharmacological screening.[77] Their team found that proteasomal inhibitor Bortezomi can trigger the MYC-related vulnerability. Their findings provided the rationale to further develop the precise targeting of the UPS as a subtype-specific therapeutic approach. In addition, some drug-based synthetic lethal vulnerabilities of MYC expression, or the upstream or downstream pathways have been identified in PDAC cell lines. In 2013, Gendre *et al*. reported that the suppression of Akt phosphorylation restored the rapamycin sensitivity in pancreatic cancer cells with defec-

tive TGF-β/Smad4 signaling.[131] Through *in vivo* CRISPR screening, Wei *et al*. reported PRMT5 as a potential combinational target to form SL with gemcitabine (Gem) in pancreatic cancer cells.[132] It was subsequently proven that the depletion of PRMT5 resulted in synergistic cytotoxicity with Gem. Their subsequent experiment supported the notion that PRMT5 inhibition leads to the depletion of replication protein A, which plays an important role in the HR process. Recently, Du *et al*. reported that the combined therapy with salirasib and Eeyarestatin I (inhibitors of RAS and the endoplasmic reticulum-associated protein degradation [ERAD] pathway, respectively) can induce a unfolded protein response, and even SL, in murine and human PDAC cells.[90] Furthermore, they found that the CRISPR-based genetic knockout of key ERAD components, HRD1 and SEL1L, can sensitize PDAC cells to salirasib.

In summary, with the introduction of the concept of SL, researchers can postulate the synthetic lethal relationship of MYC with various molecules or events previously mentioned, such as CDK1/2, Aurora kinase, BTE inhibition, and p300 inactivation, which was validated by continuous preclinical advances in other malignancies.[83,120,133–136] Despite the slow progress in the SL-based therapy of PADC, a bright prospect is well-expected, considering the strong connection between PADC and MYC overexpression. Further developments are required before these synthetic lethal targets can bring clinical benefits.

Other MYC targeting approaches

Despite the difficulty in the direct targeted therapy of MYC, researchers have attempted to directly target the MYC gene through cellular penetrating peptides, macropinocytosis, siRNA, CRISPR-Cas gene editing technology, *etc*.[137–140] In addition, various non-coding RNAs, such as circRNA, lncRNA and miRNA, were reported to participate in multiple biological processes of MYC, and regulate its function.[141–143] The modulation of these RNAs may serve as a method of targeted therapy.

Future directions

The incidence and mortality of PDAC are on the rise worldwide, attracting increasing attention from medical experts all over the world. Great progress has been made in diagnosis, treatment and basic research, but there are still many unanswered questions. The pathogenesis of PDAC remains unclear, and further research is needed. MYC is closely correlated to the progression of PDAC. This review presents the multiple mechanisms of MYC in affecting PDAC, and provides new ideas for the treatment of PDAC by acting on MYC. It was considered that further research would lead to greater discoveries in the diagnosis and treatment of PDAC.

Conclusions

Drugs that target the MYC gene transcription for PDAC, such as BETi and HDAC inhibitors, are generally entering early clinical studies. However, more efforts are needed, since there are many targets relevant to the MYC gene transcription, and that targeting a single vulnerability can easily cause the compensatory feedback of cells, leading to unsustainable efficacy and even dug resistance.

Interference with the formation of the MYC/MAX dimer is a popular research idea to inhibit the function of MYC proteins, which is expressed at a high level in the preclinical development stage. Since the MYC/MAX dimer is downstream of the MYC signaling pathway, the side effects would be much less. However, the interface of the protein-protein interaction (PPI) of the dimer is very large, making it difficult to identify suitable binding areas and methods to develop small molecular drugs. Although the interference with the PPI remains as a challenge, this presents as an opportunity for the development of drugs that target MYC/MAX.

Targeting the MYC protein ubiquitination system is a novel idea. The Aurora-A kinase inhibitor MLN8237, which was detected with the activity of inhibiting the deubiquinization system of MYC proteins, once progressed to phase I/II clinical trials. However, its development was eventually terminated due to safety issues. Finally, the development of drugs based on MYC SL is being gradually recognized and valued in the industry.

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Conflict of interest

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Author contributions

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